

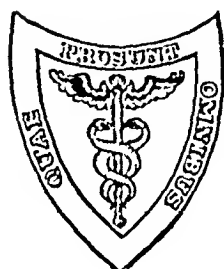
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THE
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JULY, 1941

ORIGINAL ARTICLES.

TYPES OF ORTHOSTATIC HYPOTENSION AND THEIR
TREATMENT.

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WITH changes in posture, alterations in the hydrostatic factor of the blood pressure in different parts of the vascular bed tend to produce a redistribution of the bloodflow. This would impair the circulation of vital organs such as the brain and heart, were it not for the operation of certain well known reflexes. These reflexes are called into action whenever there is a sufficient change in blood pressure in the region of receptor mechanisms located in specific areas such as the carotid sinus, the aortic arch, the mesentery and probably in other areas. The subject has been reviewed by Bronk.³

When a normal person assumes the erect position, the hydrostatic fall in blood pressure stimulates these receptor endings. Peripheral vasoconstriction occurs suddenly as the vasomotor center responds to these afferent impulses. This adaptation is so prompt that the blood pressure usually appears to be well maintained at a level similar to that observed while reclining.

In orthostatic or postural hypotension there is a considerable fall in blood pressure upon standing, often accompanied by manifesta-

tions which are presumably the result of cerebral anemia. The clear description of such a syndrome by Bradbury and Eggleston¹ has stimulated an interest in the subject. Ellis and Haynes⁸ have emphasized the frequent association of orthostatic hypotension with disease of the nervous system, and have investigated certain aspects of the abnormal physiology underlying the condition. Our report is an attempt to classify patients with orthostatic hypotension upon the basis of their reactions to tests of vasomotor function. A rationale of treatment is presented, based upon the defects believed to be important.

The effector mechanisms by which vasomotor reflexes exercise their control upon the cardiovascular system are of two types: First, reflex changes in the tone of peripheral vessels, under control of the sympathetic nerves, may alter the peripheral resistance of portions of the vascular bed. Secondly, reflex changes in the heart rate or volume ejected per beat may alter the cardiac output to meet the new situation. The relative importance of these two mechanisms has recently been studied in dogs.⁹ It was of interest to investigate these two types of vasomotor activity when elicited by a change of posture from lying to standing, both in normal subjects and in patients with orthostatic hypotension.

Methods. It was difficult to obtain a measure of the early adaptive changes which may take place in the heart. Variations in pulse rate may reflect these to a certain extent. The pulse rate was measured from the plethysmographic records to be described, or by palpation at the wrist. As an index of peripheral vasomotor effects, changes in the bloodflow through a finger were measured. Finger bloodflow has been shown to provide a sensitive index of peripheral sympathetic activity.¹⁰ The peripheral sympathetic system tends characteristically to show mass activity, producing simultaneous changes in the blood vessels of the skin in widely different parts of the body. Therefore deductions made from changes of flow in a finger are by no means limited to the behavior of that digit.

Measurements of flow were made by the plethysmographic technique of Burton.¹¹ The pulsations from a finger plethysmograph are recorded optically, utilizing a small rubber cuff placed above the plethysmograph for intermittent occlusion of the veins. Blood pressure was estimated on the opposite arm by the use of a Riva-Rocci cuff and auscultation. The subjects lay on a bed for 10 minutes, or until blood pressures were constant, after which a series of 20 or 30 determinations of blood flow were made. They then arose to stand quietly beside the bed, with the hand supported at the level of the heart. Measurements of flow and of blood pressure were then resumed immediately. Other methods occasionally employed in this study will be referred to subsequently.

Measurements of cardiac output¹² and of skin temperature,¹³ before and after assuming the erect position, have been recorded by others. It must be emphasized, however, that these measurements cannot be made quickly enough to reflect the prompt adjustments which result from reflex activity.¹³ We have employed a standard test¹⁴ of the capacity of the patient to develop vasodilatation when heat is applied to a distant extremity (to be referred to subsequently as *thermal reflex dilatation*), to serve merely as an indication of the integrity of the sympathetic nerves supplying the region tested.

I. *Normal Subjects.* Results for 6 normal subjects are shown in Figure 1. Here the mean pressure, computed as the mean of systolic and diastolic pressures, changed less than 8% between lying and standing. At the top of Chart 1 are shown single curves of flow, one just before, the other just after standing. From these are derived the changes in finger volume-pulsation, in flow (given by the initial slope of the rising curves), and in heart rate. The data shown graphically below these curves are from averages of many flow determinations for the 2 minutes immediately following the assumption of the standing position. The changes are plotted as percentages of the values obtained when lying.

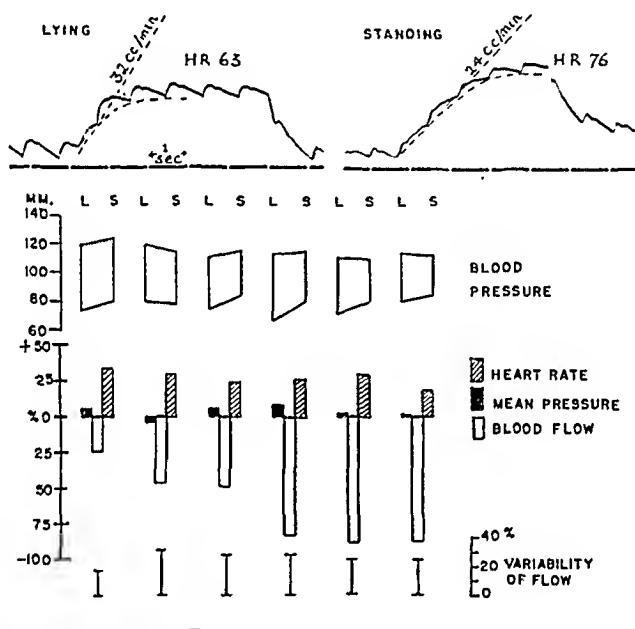


CHART 1.—Vasomotor reactions to standing in 5 normal subjects. At the top are shown samples of photographic records giving curves of bloodflow in a finger.

While there is considerable variation from one normal subject to another, there are features of the vasomotor response which were seen to be common to all. The pulse pressure usually diminished, associated with a rise in diastolic pressure and sometimes with a fall in systolic pressure. The heart rate increased by from 20 to 35%. In each case the finger bloodflow decreased markedly, in some cases by more than 80%. This decrease, by comparison with the slight changes in mean blood pressure, must indicate active constriction of the peripheral vessels. Measurements of skin temperature upon tilting a normal subject tend to confirm such vasoconstriction.¹⁵ Thus, in all of our normal subjects there was evidence of both peripheral and cardiac reflex effects, but the relative importance of the two varied greatly in different individuals. Considerable variation might also be expected in the same individual under different

environmental conditions. If, for example, the peripheral vessels were already constricted by cold, when the subject changed his position from lying to standing it might be expected that the major burden of reflex change would be borne by the cardiac mechanism, as indicated by tachycardia. It is apparent, therefore, that evidence concerning the two types of reflex activity, peripheral and cardiac, must be considered in relation to their additive effects. There is the suggestion, in Chart 1, that when tachycardia is less marked, peripheral vasoconstriction is greater, and *vice versa*.

After several minutes of standing, other adaptive mechanisms must assume importance in the task of maintaining distribution of the blood, for the heart rate tends to decrease and the finger flow to increase. Tissue pressure, as it influences venous return, is probably a larger factor.¹⁴ It is the inadequacy of these more slowly operating mechanisms that leads to syncope seen in "normal" subjects after several minutes of very quiet standing, or lying on a tilted table. In one subject we observed the initial reflex effects, but syncope intervened abruptly after a minute of standing. The abnormalities occurring with syncope of this type are probably different from those concerned in orthostatic hypotension as discussed in this paper.

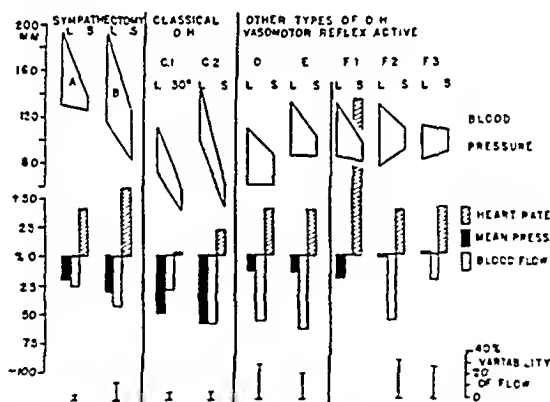


CHART 2.—Vasomotor reactions to standing, in 6 patients with orthostatic hypotension. Note absence of tachycardia in C-1 and C-2.

II. Effects of Surgical Sympathectomy. The important part played by the cardiovascular sympathetic reflexes was demonstrated by applying the same tests in cases where parts of the pathways had been interrupted. Chart 2A and 2B illustrate the reactions of 2 patients who had been subjected to surgical sympathectomy for arterial hypertension:

Patient A had just recovered from bilateral splanchnicectomy and lumbar ganglionectomy. In addition, paravertebral injections of absolute alcohol had been made by Dr. N. E. Freeman in an

attempt to interrupt the upper five thoracic rami communicantes. The decrease in finger bloodflow upon standing was not appreciably greater than would passively result from the considerable fall in blood pressure. Although the increase in heart rate was marked (accelerator mechanism not abolished by paravertebral injections), without the peripheral vasoconstriction there was a considerable fall in blood pressure.

Patient B gave evidence of cerebral damage resulting from a stroke. Following bilateral splanchnicectomy and lumbar ganglionectomy the slight decrease in finger bloodflow did not indicate active vasoconstriction in the finger. The fall in mean pressure, and increase in heart rate were even greater than shown by Patient A.

III. *Marked Impairment of Reflex Vasomotor Function—Organic Disease.* Orthostatic hypotension: Classical case.

W.L., a white man aged 45, began in 1934 to suffer from weakness, lassitude, dizziness, and attacks of unconsciousness sometimes accompanied by convulsions. These attacks were precipitated by exertion, occurred almost invariably while he was standing, and were aggravated by hot weather. They were originally considered to be idiopathic epilepsy.

In 1938 it was found that he had orthostatic hypotension.*

The patient gave no history of head injury or of syphilis or other infection. Prior to 1936 he had used both alcohol and tobacco to considerable excess. Further symptoms included loss of sexual desire and potency since 1933; intolerance to hot weather; failure to sweat save over a small area of the trunk; constipation, and pyrosis. Weakness was most marked upon arising in the mornings. No therapy had been found to give him relief.

Upon physical examination he was found to be of sthenic habitus. His complexion was usually ruddy, in contrast with the pallor said to be frequently associated with this disorder. When standing he would shuffle his feet constantly, unless he were specifically directed to the contrary. His blood pressure while lying varied from 120/70 to 150/110, his pulse from 65 to 90. Upon standing, his pulse did not accelerate, or increased by 20 beats per minute at most. The blood pressure usually fell to a level of 60/50 or lower after 1 or 2 minutes of quiet standing. The general examination was otherwise negative, save for the presence of small genitalia, and feminine distribution of pubic hair.

A neurologic examination performed April 19, 1940, by Dr. James S. Dean, revealed sluggish reactions of the pupils to light; abnormalities of associated movement and dysdiadokokinesis in the upper extremities; a disproportionate hyperreflexia in the lower extremities, with absence of normal plantar flexion and questionably positive Babinski's and Chaddock's signs on the left. These findings were interpreted to be "compatible with the presence of a considerable degree of bilateral cerebral atrophy."

An encephalogram, performed October 30, 1936, in the Temple University Hospital, was interpreted as indicating "a communicating hydrocephalus, apparently the result of arachnoid adhesions."

Repeated blood counts, urinalyses, and blood Wassermann reactions were not abnormal save for the finding of hyaline casts in a single urine specimen. Blood analyses gave the following results: blood urea nitrogen 11 mg. per 100 cc.; fasting blood sugar 76 mg. per 100 cc.; serum cholesterol

* We are indebted to Dr. John A. Reisinger, the Veterans' Administration, Washington, D. C., for this discovery, for referring the patient to us, and for allowing us to cite extensive investigations performed under his direction.

201 mg. per 100 cc.; serum proteins 6.3%; serum potassium 6.1 and calcium 11.6 milli-equivalents per liter. A glucose tolerance curve was normal. Analyses of gastric contents showed no free hydrochloric acid, and a maximum total acidity of 17 units.

The basal metabolic rate was -19% and -17% on two occasions. Repeated electrocardiograms showed left axis deviation, small *T* waves in Leads I and II, and inversion of *T* waves in Leads CF-4 and CF-5. Orthodiagrams were normal. Upon lumbar puncture no abnormalities of pressure, mechanics, chemistry or cytology were found.

During a period of observation in the University of Pennsylvania Hospital, on the service of Dr. O. H. P. Pepper, it was observed that his oral temperatures reflected that of his environment during warm weather (Chart 3). In addition, although he did not sweat spontaneously, even in a very warm room, the integrity of his sweat glands was evidenced by profuse generalized sweating after the subcutaneous injection of 10 mg. of acetyl-B-methylcholine, or 0.5 mg. of carbaminoylcholine chloride. The volume of urine secreted during the night was found to be slightly in excess of that passed during the day.

Further examinations bearing upon the abnormal physiology in this patient will be described later. A review of the literature indicates that not more than 12 cases of classical orthostatic hypotension are on record.

Chart 2, C-1 and C-2, illustrates the slight vasomotor activity shown by this patient. C-1 was obtained shortly after admission to this hospital. Since upon standing the patient was prone to lose consciousness, the test was performed by tilting his bed to an angle of 30° . Even with the very great fall in blood pressure, the increase in heart rate was insignificant, and the finger flow decreased relatively less than the mean pressure. Some months later, after treatment, the level of blood pressure while lying was higher, and the test could be made from lying to standing without fainting. Again, C-2, the diminution in finger bloodflow was not sufficiently great to indicate active vasoconstriction in spite of the marked fall in blood pressure. Nor did the degree of tachycardia correspond with the change in blood pressure.

Upon pressure over the carotid sinuses there was no change in heart rate, and the fall in systolic pressure was 10 mm. Hg. When nitroglycerin gr. 1/100 was given sublingually with the patient lying quietly, the change in heart rate was slight, the fall in blood pressure, marked: before, blood pressure 140/110, pulse 60; 10 minutes after, blood pressure 55/50 (?), pulse 78. From these tests we conclude that in this patient with classical orthostatic hypotension the vasomotor reflexes, both peripheral and cardiac, were markedly impaired.

The defects of his reflex vasomotor activity could be demonstrated in other ways: the flow of blood through the finger of a normal subject continually fluctuates between high and low values as a result of intermittent spontaneous activity of the sympathetic nervous system. Successive determinations of flow show a wide fluctuation (Chart 4-A). A measure of the degree of fluctuation is provided by the standard deviation from the mean of a series of 30 successive measurements.³ Results for this are plotted as in Charts 1 and 2. The variability amounts to between $\pm 20\%$ and $\pm 35\%$ of the mean in normal subjects. In our patient, however, the flow was remarkably constant (Chart 4-B), the standard deviation being less than 7% . In all other types examined, the variability was normal, save in the patient illustrated in Chart 2-A, who gave evidence of cerebral damage following a stroke.

Any startling stimulus, such as the prick of a pin, will elicit in the normal an intense vasoconstriction of the finger vessels (Chart 5-A). In our case of classical orthostatic hypotension this reaction was absent (Chart 5-B).

The rhythmic fluctuations of peripheral flow seen in normal persons are related to the temperature regulatory functions.⁵ It was not surprising, then, to find that our patient's regulation of body temperature was markedly deficient (Chart 3).

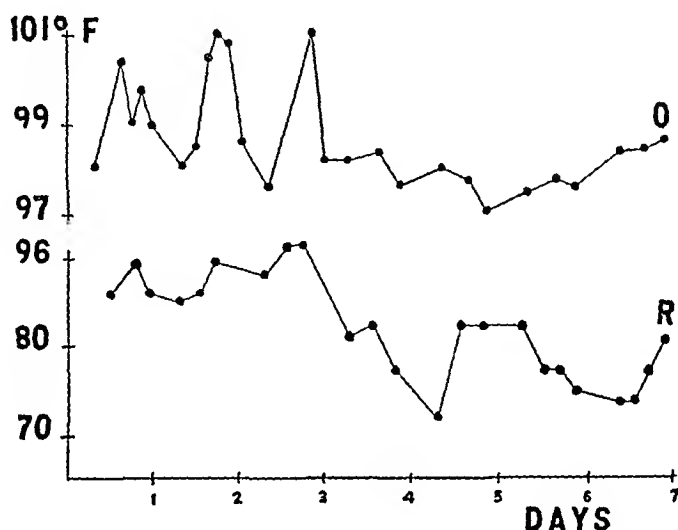


CHART 3.—Oral temperatures—*O*, of a patient with classical orthostatic hypotension, with corresponding room temperatures—*R*.

Upon heating W.L.'s legs and right hand, his left hand showed normal thermal reflex dilatation. No evidence of vasodilatation could be produced in either foot by this means, or by novocain block. We have no explanation for this discrepancy between the reactions of the upper and the lower extremities.

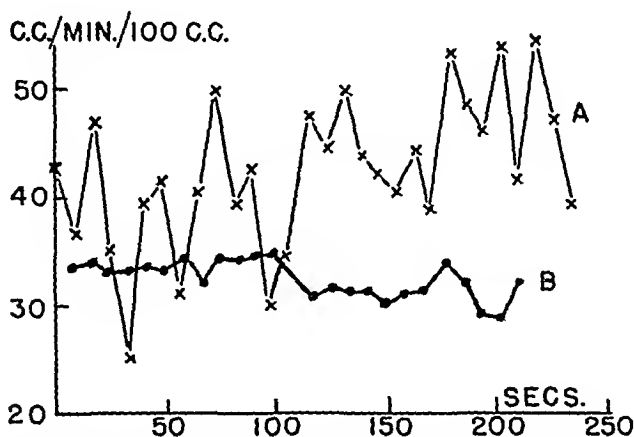


CHART 4.—Fluctuations of finger bloodflow in a normal person—*A*, and in a patient with classical orthostatic hypotension—*B*.

Central Location of Patient's Lesion: The lack of normal vaso-motor activity, both spontaneous and reflex, in classical orthostatic hypotension, might be due to widespread lesions of the peripheral sympathetic nerves, or to a lesion located centrally. Evidence, in addition to the encephalogram, suggested that the lesion was central

rather than peripheral: The psychogalvanic response to a startling stimulus is indicative of reflex activity of the sweat glands.⁶ Although W. L. showed no diminution of bloodflow, he gave a normal psychogalvanic response upon receiving such a stimulus. Anatomically, the sympathetic nerves supplying both the sweat glands and the blood-vessels lie together peripherally. The peripheral sympathetic nerves were therefore able to function. The absence of reflex vasomotor activity thus suggests that there was damage in or about the bulbar vasomotor centers.

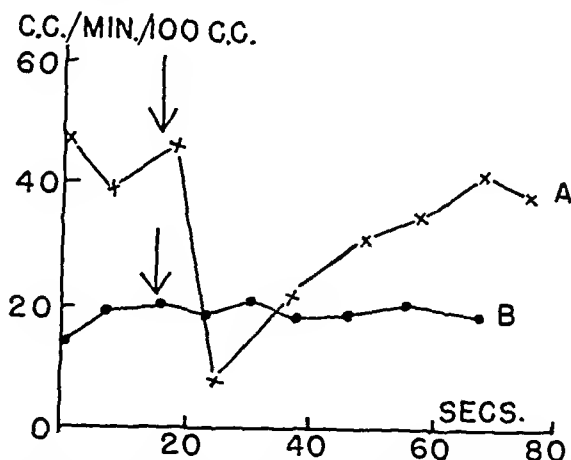


CHART 5.—Reflex vasoconstriction in the finger to a startling noise at the time marked by an arrow. A—normal subject. B—classical orthostatic hypotension.

IV. *Slight Impairment of Reflex Vasomotor Function.* A. Both Cardiac and Peripheral Mechanisms Involved: The tests which we have employed serve to distinguish the classical type of orthostatic hypotension from other cases in which there is a significant fall in blood pressure upon standing:

J.K. was a boy of 14 who had been afebrile for 9 days following lobar pneumonia, due to pneumococcus Type I, treated with sulfathiazole and type-specific serum. He was tested in the hope that he might show the fall in blood pressure upon standing which is reported to be a frequent accompaniment of convalescence from acute infectious diseases. This hope seemed amply justified, as illustrated in Chart 2-D. Despite considerable tachycardia and active vasoconstriction, there was a marked fall in blood pressure. Normal vasodilatation occurred in the toes following the application of heat to the arms, indicating no gross abnormality of the sympathetic nerves.

J.M., a young man of 18, suffered from attacks of unconsciousness with convulsions. Examinations of blood chemistry, cardiovascular structure and function, and of the central and peripheral nervous systems, revealed no obvious cause. A tentative diagnosis of idiopathic epilepsy was made. The basal metabolic rate was -32 and -38% in 1938, and -14 and -19% in 1940. His responses of blood pressure and heart rate upon standing were found to be normal in August, 1938. In June, 1940, the day following an

attack of unconsciousness and generalized convulsions, the blood pressure and pulse were discovered to be 100/70 and 60 while lying, but upon standing quietly for 2 minutes the blood pressure fell to 70/60 and the pulse rate increased to 144. The patient became pale, sweated profusely, and had to lie down because of faintness. Upon lying quietly he immediately felt better. His pulse rate and blood pressure returned to their resting values after one minute.

He was able to recall that 4 of his 6 attacks occurred during the summer months. One attack followed a game of touch football on a relatively warm winter day. On another occasion he lost consciousness while standing over a radiator, clothed warmly. Although it was not possible to obtain measurements of bloodflow, the clinical evidence suggests that his reactions were similar to those of J.K.

It seems likely that, although these patients reacted qualitatively like normal individuals, the additive effects of their tachycardia and vasoconstriction upon standing were inadequate for maintaining the blood pressure.

B. Peripheral Mechanism Impaired by Localized Lesions: In the 2 patients above, the additive effects of both cardiac and peripheral reflex activity appeared to be insufficient for maintaining the level of blood pressure upon standing. A similar inadequacy can result from lesions which affect primarily the peripheral vasomotor nerves. Ellis and Haynes⁸ have reported the frequent incidence of orthostatic hypotension among tabetics:

T.S. was a colored man, aged 56, with *tabes dorsalis*. Dr. Louis Laplace will publish his extensive observations upon this patient elsewhere, but has granted us permission to refer to the abnormalities present. Orthostatic hypotension was found occasionally and unpredictably. Half an hour before and half an hour after the test illustrated by Chart 2-E, the blood pressure was much higher (170/130) and showed no appreciable fall upon standing. Our tests indicate that there was normal acceleration of the pulse and constriction of the finger arteries accompanying the marked fall in blood pressure. Like J.K., he showed normal *thermal* reflex dilatation in his toes. The neurological abnormalities exhibited by this patient lend support to our belief that the occasional failure to maintain the level of blood pressure upon standing may have been due to transiently inadequate vasoconstriction to the lower extremities.

L.M., a white man of 25, was admitted June 11, 1940, to the neurological wards of this hospital, service of Dr. W. B. Cadwalader. Pain and weakness in both lower extremities were disabling, and had persisted after an acute onset in 1936. No arterial pulsations were palpable in the lower extremities. Signs of sensory and motor nerve abnormalities in the lower extremities were interpreted as being caused chiefly by occlusion of the aorta at its bifurcation. Measurement of skin temperatures over the lower extremities indicated an almost total lack of thermal reflex vasomotor activity. This may have been due in large part to thrombotic occlusion, despite skin warmth and color indicative of a good collateral circulation through the smaller vessels. While lying quietly his blood pressure was 138/75, pulse rate 96. Upon standing, the blood pressure fell to 110/70, the pulse accelerated to 120. Transient vertigo was noted upon standing. Examinations of finger bloodflow were not made. We believe that his mild orthostatic hypotension was due principally to deficient vasomotor control in his lower extremities.

V. *Orthostatic Hypotension Associated with Mechanical Defects in the Circulatory System.* If an abnormally great fall in blood pressure can be the result of dysfunction of the sympathetic nerves supplying the heart and blood-vessels, the same abnormality might obtain if there were mechanical defects which would nullify the activity of a normally functioning vasomotor system. Through the courtesy of Drs. W. E. Lee and N. E. Freeman, we are permitted to report our observations upon one of their patients who appeared to illustrate the latter:

B.L., a girl of 17, had a large venous angioma of the right lower extremity extending from the crest of the ilium to the sole of the foot. The right foot was swollen and painful. She was prone to faint upon standing quietly. Physical examination did not reveal important abnormalities other than the angioma. Chart 2, F-1, illustrates the enormous increase in heart rate upon standing, accompanied by a considerable fall in blood pressure. When she stood up, the volume of a small portion of her lower leg increased by 200 cc. In Chart 2, F-2, are shown the results of tying off some of the venous communications of the angioma: the blood pressure did not fall significantly, but reflex vasoconstriction was still more marked than normal. After a second operation, with further ligations, there was maintenance of blood pressure with less vasoconstriction Chart 2, F-3. At this time the volume of the lower leg increased by only 90 cc. from lying to standing. She was entirely relieved of her symptoms.

The orthostatic hypotension found in this patient seems clearly related to pooling of blood in her extensive hemangioma. There was no evidence of inadequate reflex vasomotor activity; on the contrary such activity was more marked than normal, as a compensatory mechanism. Certain other conditions under which pooling of blood is said to occur, such as arteriovenous aneurysm, pregnancy, and large varicose veins, are not often reported to be associated with orthostatic hypotension, perhaps because of a compensatory increase in blood volume: We have observed that a girl of 18, with marked cardiac enlargement due to a patent ductus arteriosus (proved at operation), responded normally to a change from the lying to the erect position.

Discussion. The Clinical Differentiation of Types of Orthostatic Hypotension: We have suggested that orthostatic hypotension might theoretically result either from inadequate reflex (a) constriction of peripheral vessels; (b) acceleration of the heart; or (c) augmentation of cardiac output. Our data have not included evidence concerning (c). Preliminary observations, using a vertical ballistocardiograph, suggests that immediately upon standing, the cardiac output of normal persons will either fall or remain constant, irrespective of the blood pressure.¹⁷ This would minimize (c) as an adaptive mechanism, and would suggest that (a) and (b) are the more important in maintaining blood pressure in normal individuals under such conditions.

While we have cited finger bloodflow as an indication of peripheral vasomotor activity, it will be seen that one can infer, within limits, the extent of such vasomotor activity from the clinical examination of the pulse and the blood pressure. If the level of blood pressure

is adequately sustained without marked tachycardia, it may be assumed that active vasoconstriction has occurred, as demonstrated in Chart 1. Conversely, if the level of blood pressure falls abnormally associated with marked tachycardia, it is probable that peripheral constriction is inadequate, unless there are mechanical faults in the circulation. This latter response is characteristic of patients who have suffered functional or structural derangement of peripheral sympathetic nerves. Finally, if orthostatic hypotension occurs without commensurate tachycardia, as in the classical cases, it is to be inferred that the cardiac accelerator pathways do not function, but the state of the peripheral sympathetics cannot be evaluated without further evidence, such as can be obtained by measurements of peripheral bloodflow.

As illustrated by the clinical cases presented, the discovery of abnormalities in the central or peripheral nerves, or of vascular thromboses, or arterio-venous shunts, may render more intelligible the interpretation of orthostatic hypotension in any given case.

We suggest, therefore, that a careful clinical examination, in the absence of more elaborate tests, will often suffice not only to diagnose the condition, but also to allow an understanding of the abnormal physiology involved and point the way to effective treatment.

Treatment. The primary objective in the treatment of orthostatic hypotension is to compensate for the tendency of the blood to gravitate to the inferior portions of the body when the patient stands erect.

Various mechanical means have been employed. Victims of this disorder soon discover the dangers of standing quietly. They learn to sway or to shift from one side to the other, as did our patient W. L., so that the pumping action of the muscles can be utilized.² Tight abdominal binders are useful. However, W. L. failed to obtain subjective or objective improvement from an abdominal binder alone, whereas there was definite relief when both legs and the abdomen were bandaged tightly. MacLean and Allen¹³ have found that symptoms upon arising are less severe in patients having orthostatic hypotension, if they will learn to sleep with their heads and shoulders elevated. On warm days strenuous physical exertion is to be avoided.

The medicinal treatment of severe degrees of this disorder has been generally disappointing, despite some rather optimistic reports.^{7,11} It should be emphasized that the low levels of blood pressure at which patients will experience vertigo or syncope may vary considerably according to the individual, the environmental temperature, and the physical activity. It seems likely that the state of the cerebral blood-vessels is also an important factor. A combination of drug actions which would lower the threshold of cerebral activity, while increasing the tone of peripheral arteries and

veins, would seem to be desirable. Such a combination is now available in amphetamine¹⁶ and paredrinol (veritol).¹⁸

In elderly persons with cerebral arteriosclerosis, symptoms may be experienced when only a slight fall in blood pressure occurs.¹⁹ For these patients, the use of a pressor drug is probably ill-advised. Actually, small doses of amphetamine, without paredrinol, will frequently be sufficient for symptomatic relief. Conversely, in younger patients with severe orthostatic hypotension, the pressor action of paredrinol is probably the most important part of their treatment.

Drugs such as epinephrine and ephedrine will assuredly raise the blood pressure, but are prone to give undesirable, side effects. W.L. could not tolerate even 5 minim doses of epinephrine subcutaneously on account of headache and palpitation. The blood pressure increased from 120/96 to 150/100, but fell to 90/60 when he stood up.

We have observed the effects of amphetamine, paredrine, paredrinol, and the isomeric constituents of amphetamine in the case of W.L. and others. Dr. John A. Reisinger has furnished us with data concerning the effects of ephedrine and neo-synephrin upon W.L. Because of the variability of his blood pressure responses it is difficult to make an accurate analysis of drug action. Suffice it to say that he felt his best, and his blood pressure seemed best sustained, when he took 10 mg. of amphetamine and 20 mg. of paredrinol orally before arising, then repeated the paredrinol at hourly intervals until 4 P.M. No untoward reactions have resulted from a year's medication according to this schedule. Repeated electrocardiograms, taken during trials with various drugs, were most nearly normal as regards *T* wave amplitude when he was taking this combination. During hot summer weather, however, this medication did not prevent the occurrence of attacks of unconsciousness with convulsions if he ventured up from the basement of his home.

Table 1 shows the most favorable responses in pulse and blood pressure obtained in the case of W.L. and others during the time when they were taking the specified drug, or combination of drugs. The least abnormal responses, without therapy, are included for comparison. Because paredrinol, *in therapeutic dosage*, is an almost purely pressor drug, having no disturbing side effects in our experience, we feel that it deserves a further trial in the treatment of orthostatic hypotension. Our experience does not permit a comparison of the clinical effectiveness of paredrinol versus paredrine. W.L. complained less of lassitude when taking paredrinol. It is apparent that in the case of classical orthostatic hypotension, medication sufficient to produce hypertension had to be given. Even then, the tendency of the blood pressure to fall was not abolished. The lower levels reached were still high enough, however, to avert the usual syncopal attacks.

TABLE 1.—EFFECT OF DRUGS UPON CARDIOVASCULAR RESPONSE TO STANDING. BEST RESPONSE, ONLY, TO DRUGS TRIED.

Pt.	Drug.	Dose per day (mg.).	Lying.		Standing.		Vertigo or faintness on standing.	Side effects.
			B.P.	Pulse.	B.P.	Pulse.		
W.L.	None	..	110/90*	80	50/45	90	++	Insomnia Insomnia Headache 0
	Amphetamine	80	145/120	80	70/55	100	0	
	d-amphetamine	30	170/115	66	65/55	90	0	
	l-amphetamine	30	150/110	78	60/50	90	+	
	Amphetamine Paredrine	80 } 80 }	110/90	78	50/?	90	+	Insomnia
	Paredrinol	200	160/110	72	70/60	90	0	0
	Amphetamine Paredrinol	10 } 160 }	160/118	66	70/58	78	0	0
L.M.	None	..	138/75*	96	112/75	120	+	
	Amphetamine Paredrinol	5 } 120 }	110/74	90	60/50	150	+++	0
	Amphetamine Paredrinol	5 } 160 }	126/78	92	92/64	124	0	0
J.M.	None	..	100/60*	66	42/38	144	++++	
	Amphetamine Paredrinol	10 } 60 }	100/60	54	110/70	90	0	0

* Marked variability from day to day.

It is perhaps only a coincidence that 2 of our patients were found to have basal metabolic rates below the limits of normal. Daily rations of thyroid substance were given to J.M. for 2 years, but it was not felt justifiable to test its effects without the simultaneous use of other therapy. The possibility of contributory endocrine dysfunction should be considered in the clinical evaluation of patients having this disorder, and treatment should be planned accordingly. In the case of W.L., the intramuscular administration of testosterone propionate, 140 mg. over a period of 8 days, resulted in no subjective or objective change.

Summary and Conclusions. 1. The physiology of adaptation to the erect position is reviewed as the basis for an understanding of orthostatic hypotension.

2. The physiologic importance of peripheral vasomotor activity, plus changes in heart rate, is emphasized.

3. A clinical study of normal subjects, patients following sympathectomy and those with orthostatic hypotension is reported, using chiefly the following criteria: blood pressure, pulse rate, digital bloodflow, and skin temperature.

4. According to their reactions to the tests above, our patients have been classified as having orthostatic hypotension due to slight, or marked impairment of reflex vasomotor function, or to mechanical defects in the circulatory system.

5. These patients showed orthostatic hypotension in association with: lesions of the central and peripheral nervous systems (communicating hydrocephalus, tabes dorsalis, and nerve injury secondary to arterial occlusion); the post infectious state; and venous angioma. In one patient (E.M.) no etiology could be discovered.

6. The clinical evaluation of patients with orthostatic hypotension is discussed and a rationale of treatment is outlined.

We gratefully acknowledge further the permission of the following physicians to make reference to their patients: Drs. F. C. Grant, I. S. Ravdin, E. A. Mallon, Temple Fay, Isaac Starr, F. J. Braceland, and C. C. Wolferth.

The Smith, Kline & French Company kindly supplied us with the following drugs: amphetamine, and its dextro- and levo- forms, paredrinol, and paredrine.

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HYPERTENSION AND THE PRESSOR ACTIVITY OF HEATED EXTRACTS OF HUMAN KIDNEYS.

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SALINE extracts of kidneys of hypertensive patients were found by Prinzmetal *et al.*^{6,7} to elevate the blood pressure of anesthetized and unanesthetized dogs by a slightly greater average amount than did similarly prepared extracts of kidneys from patients whose blood pressure was normal during life. The variation in the observed

* The expenses of this investigation were defrayed in part by a grant from the Commonwealth Fund for that portion of the work done at the University of Pennsylvania.

pressor responses was marked and the results with normal and hypertensive cases overlapped extensively. Likewise, Harrison *et al.*,² and Prinzmetal and Friedman⁶ found that simple saline extracts of kidneys from experimentally hypertensive dogs elevated the blood pressure of normal dogs to a greater degree than did extracts of normal dogs' kidneys.

On the other hand, Pickering and Prinzmetal⁵ and Beckwith and Chanutin¹ concluded that the extracts of kidneys from experimentally hypertensive rabbits and rats, respectively, exhibited less pressor activity than extracts of kidneys made from normal control animals. The last two observations^{1,5} were made with partially purified extracts, avoiding thereby the conspicuous initial fall of blood pressure which is characteristic of most simple saline extracts of kidney tissue³ and which might conceivably diminish or enhance the later pressor effects.

In view of this uncertainty concerning the pressor activity of kidney extracts it seemed advisable to extend the observations on the pressor activity of human kidney extracts, using for comparison a method of extraction³ which eliminates almost entirely the initial toxic and depressor effects. Despite these apparent advantages, the results of these experiments have proved to be even less definite than those of Prinzmetal *et al.*,^{6,7} and Harrison *et al.*² It is of interest, however, that in those few instances in which unquestioned pressor responses were obtained, peripheral bloodflow as measured by skin temperature was not diminished. In this respect the pressor substance in extracts of human kidneys resembles the renin of the rabbits' kidney and the renin-activator-angiotonin system described by Page⁴ both of which elevate blood pressure without diminishing cutaneous bloodflow.

Methods and Material. *Preliminary observations on methods of extraction and assay.* (a) Grinding the kidney tissue in a colloid mill produced more active extracts than did grinding with sand in a mortar, even when preceded by grinding in a Latapie machine. (b) Treatment of the filtered extract with appropriate concentrations of ammonium sulphate, followed by dialysis of the active fractions at pH 7.3 was not appreciably superior to heating at 55° C. for 20 minutes with subsequent filtration. The results with both methods were variable, but the average of ten comparisons favored the simpler heating method. (c) Changing the pH of the suspension to as low as 4.0 or as high as 8.0 prior to heating generally decreased, and never increased, the yield of pressor material. The pH of the crude extract was approximately 6.5 and heating at this reaction yielded most consistent results. (d) Comparison of nephrectomized and normal rabbits for assay purposes indicated that the former were preferable because pressor responses were not only greater but more consistent, agreeing with many similar observations by others on dogs.

Routine Procedure. Human kidneys were obtained at autopsy within 3 to 18 hours after death, and, in 2 instances, at operation. The entire kidney, or a radially cut portion of the kidney, including both medulla and cortex, was divided into small fragments. Enough 0.9% NaCl solution was added to make a 20% extract based on the wet weight of the kidney tissue. This mixture was ground in a colloid mill for 5 minutes, during which the temperature of the suspension did not exceed 35° C. Part of this 20% suspension was heated in a water bath at 55° C. for 20 minutes and then filtered through two layers of filter paper in funnels also heated to 55° C. This clear yellow or reddish extract was used for assay.

The remainder of the 20% crude suspension was frozen and dried from the frozen state (Cryochem process) for preservation and later use if repeated testing was indicated. For assay, rabbits weighing between 2.2 and 3.7 kilos, were anesthetized by injecting subcutaneously 1.3 cc. of paraldehyde per kilo and a bilateral nephrectomy was performed through flank incisions. Immediately thereafter the femoral artery was cannulated and connected to a Hürthle manometer writing on a smoked drum; heparin was used as the anti-coagulant. After a suitable control period (30 to 45 minutes) 20 cc. of 20% heated extract were injected into an ear vein at the rate of 1.7 cc. per minute by a motor-driven syringe. Ten minutes after the end of this initial injection, 5 cc. of a standard active 10% rabbit kidney extract was injected to determine to what degree prior injection of the human kidney extract had protected the assay animal against the pressor effect of rabbit renin. Ten minutes after this second injection the animal was killed by asphyxia and the maximum blood pressure response to this stimulus recorded, for comparison with the remainder of the record. Only one sample of human kidney extract was injected into each animal. In the early assays dosage was graded according to the body weights of the rabbits, but the results were not any more uniform than those in which a set dose was injected.

In a group of unanesthetized rabbits effects of kidney extract on blood pressure, pulse rate, and skin temperature were observed as previously described in detail.³ Blood pressures were measured in the auricular artery graphically at intervals of one minute. Injections were made painlessly through a minute T-cannula sewed in a marginal vein of the ear. Skin temperature of the opposite ear was measured by means of a thermal junction to determine whether or not peripheral bloodflow was decreased during the period when blood pressure was elevated.

The 16 "normal" kidneys were obtained at the autopsies of patients who, during life, had blood pressures of 80 to 120 mm. Hg systolic, and 50 to 80 mm. Hg diastolic, and presented no anatomic evidence of renal disease. The abnormal kidneys used can be divided into three groups: (a) 7 cases of chronic glomerulonephritis with blood pressures during life ranging from 160 to 190 mm. Hg systolic and from 90 to 136 mm. Hg diastolic; (b) 15 cases of benign hypertension with blood pressures during life ranging from 150 to 300 mm. Hg systolic, and from 90 to 140 mm. Hg diastolic; and (c) 14 cases of malignant nephrosclerosis with blood pressures during life ranging from 200 to 280 mm. Hg systolic and from 130 to 180 mm. Hg diastolic. The cases chosen for study had histories quite typical of their respective anatomic diagnoses. This last group includes 2 cases of hypertension in which a unilateral nephrectomy was performed because of (a) anomaly and atrophy, and (b) unilateral pyelonephritis.

Observations. In rabbits the slow intravenous injection of simple saline extracts of normal and abnormal human kidneys was often lethal and almost always strikingly depressor, even after careful filtration and centrifugation. The lowering of blood pressure was

accompanied by conspicuous blanching of the ear, dyspnea, tachycardia, and usually a few convulsive movements before death. Therefore the rabbit appears to be more sensitive than dogs or rats^{2,6,7} to the toxic and depressor fractions of these crude extracts. On the other hand, freshly prepared heated extracts of human kidneys did not depress blood pressure and were never lethal when injected immediately after heating and filtration. After standing at room temperature for several hours or in the refrigerator for 24 hours, a previously innocuous extract usually became depressor or even lethal once more. These effects could be abolished again by re-heating.

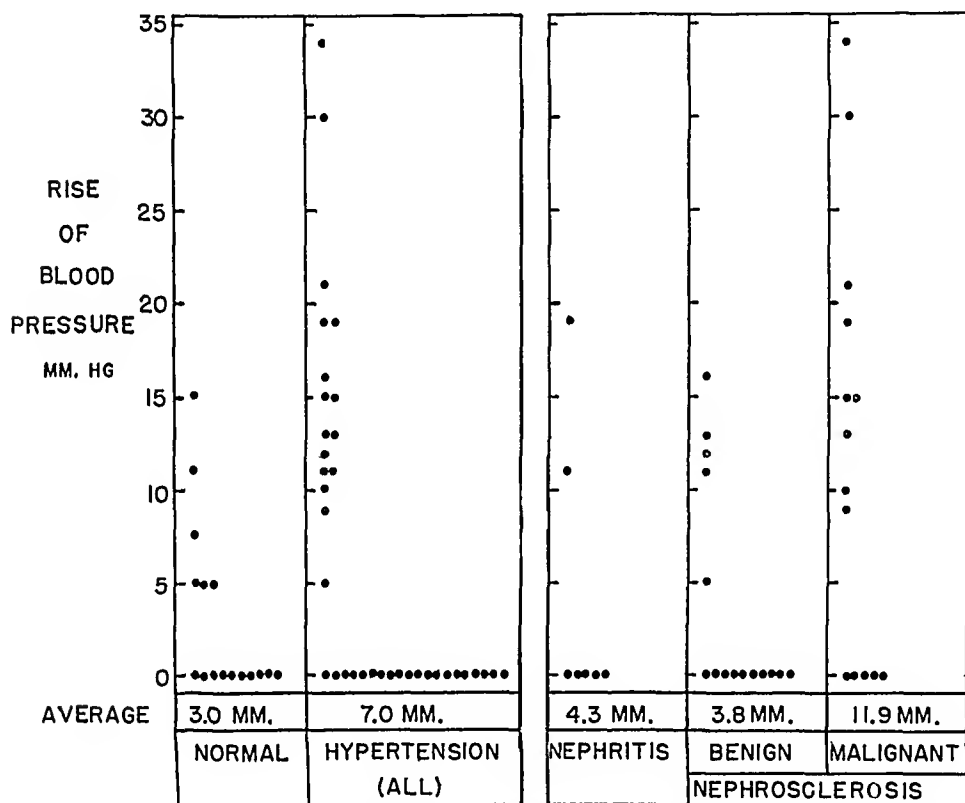


CHART 1.—Pressor activity of heated human kidney extracts, normal and hypertensive cases. To the right the latter are divided into three categories. Each dot represents 1 case.

The heated kidney extracts were either entirely inert producing no perceptible effect on blood pressure or pulse rate, or they were moderately pressor in some instances. Active extracts produced their maximal effect on blood pressure in 2 to 5 minutes; the elevation persisted for 30 to 45 minutes or until the record was interrupted by the injection of rabbit kidney extract at the end of 10 minutes.

The results produced in anesthetized nephrectomized rabbits are summarized in Chart 1. Of 16 extracts prepared from normal kidneys, 10 were inert and the remaining 6 elevated blood pressure by

between 5 to 15 mm. Hg. In the entire hypertensive group, consisting of 36 extracts, 20 were inert, while 16 raised blood pressure by between 5 and 34 mm. Hg. To the right in Chart 1 the hypertensive group has been subdivided according to diagnosis. No difference could be demonstrated in the pressor activity exhibited by extracts of normal kidneys and of those from cases of glomerulonephritis and benign hypertension.

In those cases dying of malignant nephrosclerosis, in the third or fourth decade, 9 of the 14 extracts were active and 5 were inactive. The slightly greater proportion of positive results the greater magnitude of certain of these responses in general, and the higher average observed may conceivably suggest a greater renin content in this group. Yet no quantitative relationship could be demonstrated between the height of the patients' blood pressures during life and the pressor activity of their respective heated kidney extracts. Some of the inert extracts, including the 2 prepared from kidneys removed at operation, came from cases with blood pressure even higher than those providing definitely pressor extracts. While 4, and possibly 6, extracts in the cases of malignant nephrosclerosis produced pressor responses outside the range observed with extracts of normal kidneys, the variation is so great that average figures mean little. Nor did it seem likely that a greater number of assays by this method could produce any more definite conclusion.

As mentioned under *methods*, the injection of human kidney extract into each nephrectomized rabbit was followed 10 minutes later by the injection of a standard dose of heated rabbit kidney extract for the purpose of detecting the presence of protective or anti-pressor effect in the extracts of human kidneys. Extracts from 3 normal kidneys strikingly reduced the effect of the subsequent injections of rabbit renin, but the remainder reduced the effect of the latter injection only slightly or not at all. The extracts from hypertensive kidneys showed similar wide variation of protective effect. The average protection afforded by the extracts from kidneys of hypertensive cases was slightly less than that accorded by the normal extracts, but again the range of variation was too great to conclude that a real difference existed. Nor was there any consistently inverse relation between pressor activity and protective action. Comparison of the pressor and anti-pressor assays with the rise of blood pressure during asphyxia did not modify these conclusions.

Finally, to test the nature of the pressor substance in human kidney extracts, 10 samples which elevated the blood pressure of anesthetized, nephrectomized rabbits by between 10 and 34 mm. Hg were injected also into unanesthetized rabbits. Five of these extracts, though pressor for nephrectomized rabbits, had no effect on the blood pressure of the unanesthetized rabbits, presumably

because of the protective action of normal functioning kidneys. The other 5, however, elevated blood pressure by 5 to 25 mm. Hg, without diminishing peripheral bloodflow. The effects of these few active human kidney extracts were therefore similar to those of renin, as observed previously for heated rabbit kidney extracts³ and in the renin-activator-angiotonin system described by Page.⁴

Comment and Conclusions. The results indicate that renin is present in small amounts in some human kidney extracts and produces the characteristic rise of blood pressure without reduction of peripheral bloodflow in the rabbit's ear. However, if renin is produced in excess by the diseased kidneys of hypertensive individuals, the inability to demonstrate greater content in those kidneys indicates either rapid passage of the substance into the blood stream, or rapid inactivation after death by autolysis or by substances in kidney tissue which destroy renin. These findings are in agreement with the recent observations of Beckwith and Chanutin¹ in rats. It would appear that present methods, while yielding suggestive results, do not demonstrate any clear relation between blood pressure during life and the renin content of kidney tissue after death. This conclusion does not in any way invalidate the humoral hypothesis of hypertension but emphasizes the necessity of studying active substances in blood during life for clear differentiation.

Summary. Heated kidney extracts were prepared from tissue obtained at autopsies of 16 cases with normal blood pressure during life and of 34 cases with marked hypertension. Anesthetized, nephrectomized rabbits were used for assay. Kidney extracts prepared from cases of benign hypertension and chronic glomerulonephritis were not more active than those of normal kidneys. The four extracts which showed pressor activity outside the normal range all came from cases of malignant nephrosclerosis. Nevertheless, the variations in activity, even in this group, make it impossible to demonstrate by these methods any clear relation between blood pressure during life and the renin content of kidney tissue after death.

The rise in blood pressure produced by active extracts of human kidneys is similar to that observed with renin from other species in that the blood pressure of the unanesthetized rabbit rises without a decrease of peripheral bloodflow.

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SUSTAINED HYPERTENSION FOLLOWING EXPERIMENTAL UNILATERAL RENAL INJURIES. EFFECTS OF NEPHRECTOMY.* †

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WILSON AND BYROM¹² were able to produce sustained hypertension as well as necrotic vascular lesions in rats by partially occluding one renal artery. We have also produced prolonged hypertension, using a different type of renal injury, and in addition found that the blood pressure, once elevated, does not quite return to the initial level after resection of the injured kidney.

Method. Albino rats weighing between 120 and 175 gm. were used in this experiment. Hypertension was produced by enveloping one kidney loosely in a V-shaped strip of cellophane.^{7,8} At the same time a thin slice of the pole of the opposite kidney (less than 10%) was removed for microscopic examination in half of the animals. Some of the rats died after developing hypertension or were sacrificed for histologic studies. Those surviving were observed for a period of 1 to 6 months. The cellophane wrapping together with the inclosed kidney was then removed through an abdominal incision under ether anesthesia and the changes in the blood pressures recorded for another period of 1 to 4 months.

A control series of 24 rats was studied for the effects on the blood pressure of unilateral nephrectomy with and without biopsy of the opposite kidney. Similar observations were made on 5 male rats whose testes were enveloped in cellophane.

Urea nitrogen in the blood was determined by a gasometric urease method suitable for whole blood.⁸ Values for normal rats with this method ranged between 10 and 30 mg. per 100 cc.

The blood pressure was measured in the tail by means of the plethysmographic method of Williams, Harrison, and Grollman.¹¹ With standardized precautions for heating the animals we have found this method to be efficient and accurate.

The blood pressure usually began to rise within 14 days after application of the cellophane, attaining in about 60 days a peak which was maintained with slight fluctuations for a period of at least 6 months or as long as the injured kidney remained *in situ*. The maximum pressure level was determined by the average of all consecutive readings for a period of 3 weeks

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at the peak of the curve. The maximum rise in blood pressure was calculated as the difference between the maximum blood pressure level and the average preoperative blood pressure. The level after nephrectomy was computed by taking the average of all of the readings beginning 3 days after operation. The course of the blood pressure in a single representative experiment is shown in Figure 1.

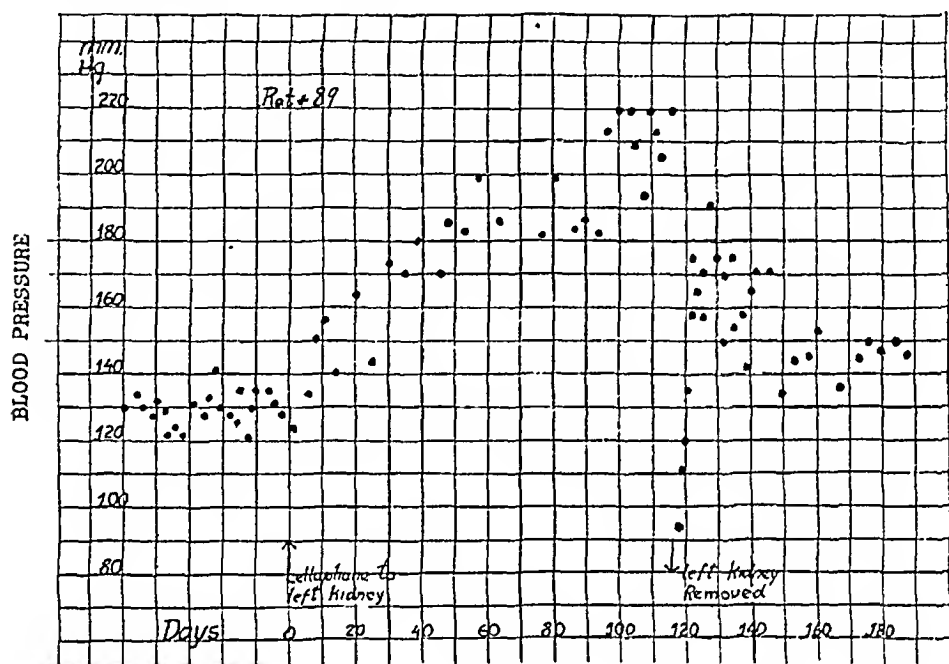


FIG. 1.—Hypertension due to cellophane perinephritis and maintenance of elevated pressure after nephrectomy.

Results. The pertinent data on 91 rats are recorded in Table 1. The maximum rise in blood pressure following unilateral cellophane perinephritis ranged from 0 to 100 mm. Hg (mean, 44 mm.). The hypertension was maintained in most of the animals throughout the period of observation, the longest period being 6 months. Failure to develop sustained hypertension was generally associated with one of the following conditions: tearing or slipping of the cellophane envelope; too tight application of the cellophane resulting in complete ischemic necrosis of the kidney; and emaciation or illness.

The cellophane-wrapped kidney was successfully removed from 44 rats. The blood pressures, if previously elevated declined promptly after operation, but seldom attained the pre-hypertensive level. Usually they remained elevated at varying points as high as 30 mm. above the average initial pressure. Frequently dense perinephric adhesions led to considerable trauma and shock during nephrectomy. In these instances a sharp fall in blood pressure occurred immediately after operation followed by a gradual rise to a point up to or above the pre-hypertensive level, and in one rat (No. 81) above even the hypertensive level. The detailed readings

TABLE 1.—HYPERTENSION AND VASCULAR LESIONS FOLLOWING UNILATERAL RENAL INJURIES AND CHANGES IN BLOOD PRESSURE AFTER REMOVAL OF THE INJURED KIDNEYS.

Rat.	Average initial B.P. level, mm. Hg.	After wrapping one kidney in cellophane.			After removal of cellophane-wrapped kidney.		Vascular lesions.
		Maximum rise in B.P., mm. Hg.	Duration of hypertension, days.†	Urea N, mg. per 100 cc.	Change from initial B.P. level, mm. Hg.	Period of observation, days after nephrectomy.	
1*	132	0	75				
2	124	1	64	0
3	127	6	103	0
4	134	7	88	20			
5*	129	7	90	36	- 4	73	
6*	138	10	90	30			
7	140	10	137				
8	140	10	117				
9*	139	11	28	...	+ 1	120	
10*	135	12	120	19	+ 6	51	0
11*	144	14	64	...	- 3	120	
12*	154	14	77				
13	140	15	90	...	- 1	120	
14	130	15	115	0
15	127	17	89				
16	138	22	34	...	+ 7	60	
17*	120	23	85	...	+ 9	90	
18*	133	25	131	...	+10	62	0
19*	134	25	67	...	+ 8	120	0
20*	122	28	65	...	+ 9	120	0
21	120	29	131	...	+ 9	68	0
22*	136	29	70	...	+14	117	
23*	135	30	70	0
24*	135	30	40				
25	112	30	37	17			
26	137	30	31	0
27*	137	31	62	19	+15	44	0
28	121	32	30	31			
29	121	32	24				
30	127	33	112	13	+25	40	0
31	136	34	101	...	+ 6	40	0
32*	134	34	90	18	+23	45	0
33*	126	34	116	14	+11	45	0
34*	144	35	56	...	+12	45	
35*	139	35	94	0
36*	135	35	16				
37	128	35	34	0
38	125	35	128	17			
39*	140	36	69	...	+ 4	35	0
40*	121	37	140				
41*	133	38	63	16	+19	120	0
42	121	39	94	15	+21	42	0
43*	139	40	100	21	+17	20	0
44	123	41	38	0
45*	144	44	64	18	+22	120	0
46*	142	44	13				
47	141	43	101	18	+12	48	0
48	130	44	107	17	+22	45	0
49	140	45	107	13	+ 7	40	0
50	130	45	189	...	+20	72	
51*	133	44	65	15	+15	120	0

TABLE 1.—*Continued*

Rat.	Average initial B.P. level, mm. Hg.	After wrapping one kidney in cellophane.			After removal of cellophane-wrapped kidney.		Vascular lesions.
		Maximum rise in B.P., mm. Hg.	Duration of hypertension, days.†	Urea N, mg. per 100 cc.	Change from initial B.P. level, mm. Hg.	Period of observation, days after nephrectomy.	
52*	145	45	40	18	+
53*	139	46	122	21	+
54	116	46	130	31	0
55	131	47	41	0
56	130	47	107	12	+ 8	41	0
57*	130	47	110	27	+ 7	39	0
58	121	49	48	0
59	128	50	17	+
60*	130	51	115	...	+16	72	0
61	125	52	111	22	0
62	128	52	34	+
63	128	52	10	0
64	127	53	25	0
65*	141	54	36	0
66*	139	54	64	...	+13	115	0
67*	129	55	35	...	+30	40	0
68	135	55	111	...	+18	72	0
69	110	55	163	0
70	115	56	220	146	0
71	141	59	53	36	0
72	129	61	25	28	+
73*	144	63	65	20	+
74*	127	65	50	35	+13	60	0
75*	120	62	65	...	+22	96	0
76	158	67	38	20	+
77*	131	69	75	0
78*	73	71	60	17	- 1	115	0
79*	127	73	71	+
80*	124	61	118	...	+28	105	0
81	136	74	93	23	+72	30	+
82*	132	76	80	15	+17	6	+
83*	134	76	60	...	+30	120	+
84	120	77	97	25	+
85*	114	78	77	...	+15	92	+
86	110	80	80	17	+
87*	117	80	41	16	+29	70	0
88*	132	82	36	20	+
89	128	87	100	19	+30	56	0
90	122	98	90	17	+
91*	135	100	51	78	+

* Biopsy taken.

† Rats 1 to 15 from operation to death.

in 3 animals are shown graphically in Figure 2. In 5 instances there was observed after nephrectomy a decline or no change as compared with the initial blood pressure. Four of these (Nos. 5, 9, 11, 13) occurred in rats with little or no rise in pressure after application of cellophane.

The height of the blood pressure after nephrectomy in the hypertensive animals seemed in general to vary directly with the severity

of the preëxisting hypertension. This is illustrated graphically in Figure 3, which plots the relation in each animal between the maxi-

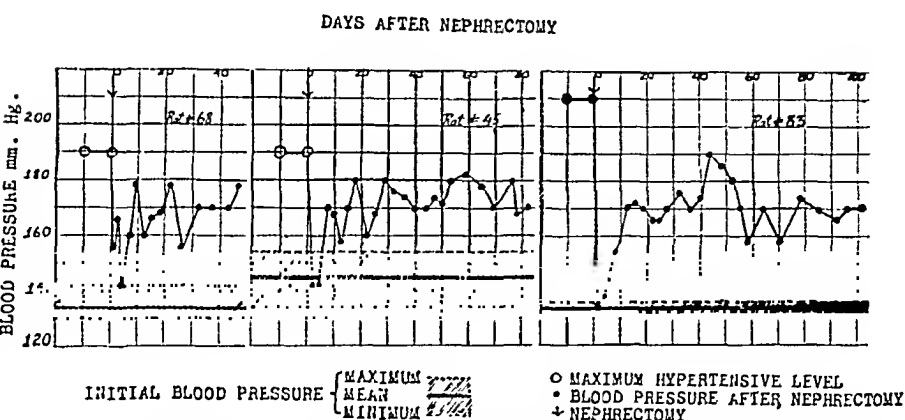


FIG. 2.—Changes in blood pressure following removal of the affected kidneys in rats with hypertension due to unilateral renal injuries.

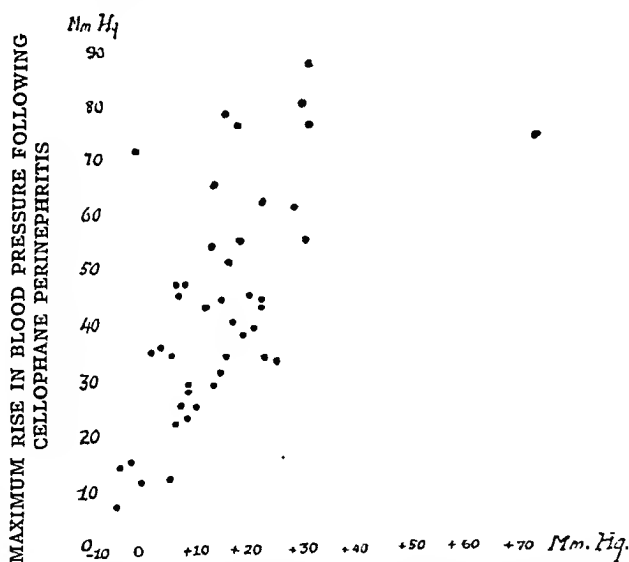


FIG. 3.—Relationship between the blood pressure level after removal of the injured kidney to the severity of the preëxisting hypertension.

imum rise in pressure following renal injury to the change in pressure over the initial level after excision of the injured kidney.

The duration of hypertension, within the limits of this experiment

did not appear to influence the level of blood pressure after nephrectomy. Equally marked effects were observed in rats with hypertension of 30 days, as in those of 120 days' duration.

Twenty-four control rats (12 of which had had preliminary biopsies of one kidney) showed no tendency toward an increase in blood pressure level when a completely intact kidney was excised (Fig. 4). No changes in blood pressure were noted in the animals with periorchitis due to cellophane.

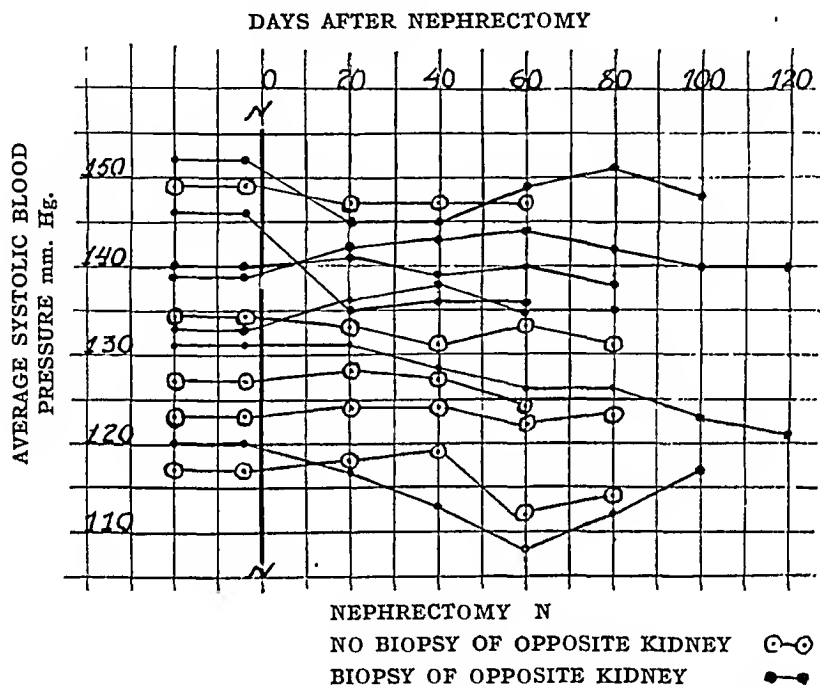


Fig. 4.—Changes in blood pressure following nephrectomy in normal rats.

The kidneys which were enclosed in cellophane appeared considerably reduced in size despite the development of a dense perinephric capsule. Inflammatory invasion of the cortex resulted in varying degrees of interstitial nephritis. Hyalinized, necrotic and inflammatory vascular lesions were observed in 20% of the rats involving the medium sized and small arteries and arterioles of the pancreas, mesentery, intestines, heart, testes and of the unoperated kidney (Fig. 5). No arterial lesions were found in the lungs or in the kidney within the cellophane capsule. The intense inflammatory and necrotic arterial and arteriolar lesions were confined to the animals that had had a severe and rapid rise in blood pressure (more than 45 mm. Hg). Their presence did not appear to be related to the duration of hypertension or to the degree of renal insufficiency. Of the 12 rats with severe vascular lesions in which tests for urea nitrogen of the blood were carried out only 2 showed values for urea above the normal limits. One rat (No. 70) had marked nitrogen retention without vascular lesions.

The vessels in the intact kidneys of the hypertensive animals that survived nephrectomy were compared with those of normal rats (and in some cases with those in the place of their own kidney removed as biopsy). Striking differences were observed in only 2 instances.



FIG. 5.—Vascular changes in rats with hypertension due to unilateral renal injury. *A*, Intact kidney. Hyalinization of an afferent arteriole. H & E stain. ($\times 260$.) *B*, Intact kidney. Cellular intimal proliferation of a small interlobular artery. H & E stain. ($\times 260$.) *C*, Pancreas. Subintimal fibrinoid necrosis of small artery. H & E stain. ($\times 260$.) *D*, Intestine. Subintimal fibrinoid necrosis of a small submucosal artery. H & E stain. ($\times 260$.)

Discussion. The effectiveness of the cellophane envelope in producing hypertension may be attributed to a combination of factors exercising varying rôles in different animals: 1, Constricting effect of the dense perinephritic capsule; 2, constricting action on

the hilar structures with arterial, venous, and ureteral obstruction; 3, prevention of collateral circulation through the cortex; 4, inflammation of the kidney substance due to a foreign body.

Our observations with cellophane are in complete agreement with those of Wilson and Byrom¹² who employed arterial clamps. Sustained hypertension as well as arterial lesions may be produced in the rat by an injury to one kidney using either method, the contralateral kidney remaining intact. In these respects the findings in the rat appear to differ from the general experience with experimental hypertension in the dog and rabbit. Prolonged hypertension resulting from unilateral renal lesions was observed in occasional dogs by Goldblatt^{3b} and Wood and Cash¹³ and in rabbits by Drury.² They did not note severely hyalinized and necrotic vascular lesions in animals with an intact kidney.^{3a,9} Our data indicate that the presence of renal insufficiency is not an essential factor for the development of these lesions. They agree with those of previous observers,^{3a,9,12} who emphasized the importance of a rapidly developing severe elevation of blood pressure.

Maintenance of an elevated blood pressure after removal of the injured kidney in a hypertensive animal has not previously been reported. It cannot be attributed to loss of kidney substance because it did not occur in nephrectomized non-hypertensive rats. We did not observe significant rises in blood pressure levels over a period of one year in normal rats of a corresponding age group, so that changes due to ageing may be considered negligible. Grossman and Williams⁴ recorded blood pressures by direct arterial cannulation in rats varying in age from 2 months to 2½ years and found no consistent differences in this range. The influence of cellophane as a foreign body may be disregarded, since the changes did not occur in all the animals and were not noted in rats with similar injuries to the testicles.

The new level of pressure after nephrectomy does not represent a transitional phase between the hypertensive and normal points. It was sustained for a period of 3 or 4 months or longer, showing no tendency to decline and occasionally even rising gradually toward the hypertensive level.

The persistence of an elevated pressure long after the original stimulus has been removed suggests that irreversible changes have been induced. We have no evidence concerning the nature of these alterations other than those previously described in the vessels. The presence of arterial and arteriolar lesions in the unoperated, presumably normal kidney may serve to establish new areas of renal ischemia; while their occurrence in an extensive splanchnic vascular bed may act as a contributing factor in maintaining an elevated blood pressure. The findings of Blalock and Levy¹ are of interest in this connection. They succeeded in producing complete occlusion of the coeliac axis and the superior and inferior mesenteric arteries in

dogs and noted a sustained elevation in blood pressure in some animals.

Extensive anatomic changes in the vessels were seen in only a small fraction of our animals and may have no causal relation to the elevated blood pressure. It is conceivable that an increase in peripheral resistance might occur due to narrowing of the vascular bed which is too minute to be detected microscopically. The resistance to flow varies inversely as the square of the radius of the vessel, so that a small change in lumen can effect a proportionately larger change in resistance.

There have accumulated in recent years a number of reports bearing on the association of hypertension with unilateral renal disease in humans and on the course of the blood pressure following excision of the diseased kidney. Schroeder and Fish¹⁰ reviewed the cases in the literature and added 7 of their own. Additional cases were reported by Nesbit and Ratliff⁵ and by Oppenheimer, Klemperer and Moschkowitz.⁶ All authors agree that nephrectomy was frequently followed by symptomatic improvement. A decline in blood pressure was observed often after operation but was either transient or else rarely attained a level which could be considered normal for the patients' age. Of the 28 subjects reported all but 6 remained actually or potentially hypertensive after nephrectomy.

In this respect the observations in humans parallel those in our hypertensive rats. Neither in the experimental animal nor in the hypertensive patient with unilateral renal disease can one expect to obtain a "normal" blood pressure by removing the diseased kidney. We do not imply that nephrectomy is therefore bound to be fruitless as far as the hypertension is concerned. On the contrary, evidence presented indicates that an injury to a single kidney, resulting in hypertension, may lead to systemic changes which operate independently of the injured kidney in a manner to maintain an elevated blood pressure.

Summary. 1. Sustained hypertension was produced in rats by means of unilateral renal injury (perinephritis from enveloping the kidney in a cellophane envelope).

2. Hyalinized and necrotic vascular lesions were observed in some animals. Their presence was associated with rapidly rising severe hypertension but was not related to the duration of hypertension or to the presence of nitrogen retention.

3. Removal of the injured kidney from the hypertensive animals resulted in a decline in blood pressure, not to the pre-hypertensive level, but to some point above it depending upon the severity of the hypertension. Maintenance of an elevated pressure long after removal of the injured kidney suggests that irreversible changes have occurred which may or may not be related to the changes in the vessels.

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THE GERIATRIC ASPECT OF PULMONARY TUBERCULOSIS.

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It is unwise to make elaborate studies of pulmonary tuberculosis in the younger and healthier fractions of the population while neglecting the old age groups where contact is known to exist. Tuberculosis in these older persons reflects the presence of yesterday's epidemiology in today's society.

At present, the average fatal case of pulmonary tuberculosis occurs in an individual who is several years older than he would have been if the sequence of events had occurred a generation ago. The graph of tuberculosis mortality shows a falling peak in early years and rising peaks in later decades. The swing of the disease across the age span requires recognition in order to reduce the dispersion of the infection from old to young, and to elaborate methods of attacking the disease in the older individual. It would seem as if the infection, slowly being thwarted as a disease, is making headway in old tissues because methods successfully applied in young persons are not as adaptable in the older person. Every new case of tuberculosis is a demerit chalked up in vital statistic records to signify that there are still unstopped loopholes.

There is no question of the frequency of pulmonary tuberculosis in the higher ages. However, it is quite possible that the type of management in this group may constitute one of the most important obstacles to eventual success in curtailing the disease generally. The particular elements common to the older age bracket may be summarized as: the different reaction of the older body to the

tubercle bacillus; the longer period in which the infection may have been present; economic considerations; the welfare of the younger members of society; the general difficulties in controlling older patients; and the lack of an efficient medical and social approach to this problem. If to those growing old, pulmonary tuberculosis is an insidious personal matter, it still remains one of the major unsolved health problems of the present day. Any effective approach to this problem must eliminate the present common attitude of simply sighing at the aged tuberculous patient with positive sputum.

This study includes 3000 consecutive postmortem examinations done at the Philadelphia General Hospital during 1936 and 1937. Of the group reviewed, about one-third were 60 years and over, totalling approximately 1000 individuals. The ratio of white to negroes above 60 was 3 to 2. The male and female groups were approximately equal in number.

For general statistical application, pulmonary tuberculosis was classified as: 1, fibro-ulcerative; 2, miliary; and, 3, healed fibroid. The less usual varieties of the active form were incorporated in these groups to avoid over-elaboration. Taubert,²⁴ found all forms of the disease in the higher age group. Stanganelli²³ gives a much fuller classification, but the purpose is served by using the three groups named.

Excluding the primary tuberculous complex in the series, it was found that tuberculosis of the lungs occurred in 757 patients, which is 25% of the general dead that came to autopsy in the period mentioned.

In the *fibro-ulcerative group* of 462, there were 52 patients (11.2%) in the age bracket of 60 years and over. Schlesinger²² in a series of 1800 autopsies, found that 9% of active tuberculosis occurred in older persons. The important unknown is: how much tuberculosis is disseminated in the general population by this 11.2%? If the figures were applied to the general population, it would indicate that 5% of all persons 60 years and over have active tuberculosis (*i. e.*, 52 in 1000 general autopsies) though of course it is recognized that our material does not constitute a fair sampling of the population (see Table 1).

TABLE 1.—FIBRO-ULCERATIVE GROUP.

			Ratio of whites to negroes.					
			Over 60 1000 autopsies.			Under 60 2000 autopsies.		
	Total.	Under 60.	Over 60.	No. auts.	With tb.	Cor- rected.	No. auts.	With tb.
Total . .	462	410	52	3:1	3:1	1:1	3:2	2:3
White . .	200	160	40					
Negro . .	262	250	12					

In the *miliary group* (referring only to miliary pulmonary tuberculosis and not to the more common terminal miliary spread) there

were 60 patients, of whom 51 died of the disease. Of this number, 5 were 60 years and over, an incidence of 8.3%. Both Banyai¹ and Baudot² regarded this form as rare in older persons, while Braun³ found an incidence of 14%. von Rosen's²⁶ figure for the occurrence of the miliary type in general autopsies was 0.5% to 1.5%. Rich²⁰ and Follis observed that "miliary tuberculosis tends to be a much more frequent complication of pulmonary tuberculosis in old age than at any other period of adult life." The present figures show that one older person in 200 has miliary tuberculosis, in agreement with the limits of von Rosen's statistics.

TABLE 2.—MILIARY GROUP.

			Ratio of whites to negroes.					
			Over 60 1000 autopsies.			Under 60 2000 autopsies.		
	Total.	Under 60.	Over 60.	No. auts.	With tb.	Cor- rected.	No. auts.	With tb.
Total . .	60	55	5	3:1	3:2	1:2	3:2	1:6
White . .	11	8	3					1:9
Negro . .	49	47	2					

The figures show that this form of tuberculosis does not spare the older patient since one-twelfth of the total number occurred in the higher age group. The older negro is less prone to this form than is the younger of his race, but is more liable to have it than is the white member of his own generation. The young white is far less liable to the miliary form than is the young negro.

In the *healed fibroid group*, there were 235 patients. The cause of death in order of frequency of occurrence was heart disease, cancer, pneumonia, cerebral vascular accidents, and renal failure. In those of the fibro-ulcerative group who did not die of tuberculosis, cancer was more common than heart disease as the cause of death. Of the 235 patients, 153 (65%) were 60 years and over. If this figure could be applied to the general older population, it would signify that 15 of every 100 persons 60 years and over has healed fibroid pulmonary tuberculosis. This is in accurate agreement with Schlesinger's findings.²²

TABLE 3.—HEALED FIBROID FORM.

			Ratio of whites to negroes.					
			Over 60 1000 autopsies.			Under 60 2000 autopsies.		
	Total.	Under 60.	Over 60.	No. auts.	With tb.	Cor- rected.	No. auts.	With tb.
Total . .	235	82	153	3:1	9:1	3:1	3:2	2:1
White . .	192	55	137					4:3
Negro . .	43	27	16					

In summary, these figures reveal that a fair percentage of both fibro-ulcerative and miliary pulmonary tuberculosis and a very large percentage of the healed fibroid form, occurs in persons 60 years and over. As to race, there is no difference in the fibro-ulcerative,

predominance to a slight degree of the miliary in the older negro, and marked predominance of the healed fibroid type in older white persons.

The keynote of the geriatric approach to pulmonary tuberculosis is that there has not been general appreciation of the frequency of the disease in older persons.^{1,2,4,8,10,13,16b,17-19,21-24} It is interesting that Osler's¹⁹ studies were made at this hospital a half century ago. He wrote that "at the Philadelphia Hospital, in bodies of aged persons from the almshouse, it was extremely common to find either old or recent tuberculosis." The reason for such frequency is due to the combination of three contributing groups: 1, those in whom the disease was diagnosed in early life, treated successfully, and obtaining a normal tenure; 2, those in whom there was no early diagnosis due to self-neglect or inadequate study; and 3, those in whom there were no marked clinical manifestations of the disease until later life, or who contracted the disease then. Of the third group, it may be that the tuberculosis is of recent date, but due to the changed physiology of the elderly body, it evokes a proliferative rather than an exudative response. Such a body response could make *recent* disease look like an *old* condition. Banyai's¹ fine study begins on the note that old age changes alter the type of body reaction. Probably it is true that the disease may be carried through life in various phases of activity or inactivity, or that it may be contracted in later life with altered response to the infection. The three groups enumerated include all forms. It is not to be inferred from this that reference is being made to the initial entrance of the tubercle bacillus into the body, but rather to that form which is the usual clinical manifestation of the disease.

Having established figures at this hospital for the incidence of pulmonary tuberculosis in older persons by comparison with the younger group, and correcting the ratios for racial differences, we investigated the protocols of 136 individuals 60 years and over who had been diagnosed as tuberculous and studied on the tuberculosis wards.

Family History. Of the 136, 80 had noted the family history more completely than a few routine questions. Thirty-five (26%) reported known tuberculosis in older members of the family. In Myers'¹⁷ group of 37 patients, the family history was positive in 24% for the preceding generation, and in 35% of the following generation. Roentgen examination of 173 persons 65 years and over in a New Jersey County disclosed 13 persons with active pulmonary tuberculosis, one of whom had 14 Mantoux positive grandchildren.

Symptoms. There is a tendency toward understatement of the manner in which pulmonary tuberculosis presents itself in the older patient. In some, the clinical picture is as vivid as that observed in the younger decades; in others, there may be few or no symptoms. Is it necessary to recognize a new façade to this old structure, or

will old landmarks serve? The following is a tabulation of the symptoms of this group:

	Per cent.
Cough	95
Expectoration	87
Loss of weight	82
Fatigue and weakness	72
Dyspnea	68
Hemorrhage	46
Loss of appetite	42
Night sweats	35

With the exception of hemorrhage and night sweats, any or all of the other complaints could be ascribed to the debilitation of increasing age. It is quite likely that this facile conclusion is responsible for the failure to diagnose cases. The diagnostician must become conditioned to the thought that if he is dealing with this train of symptoms in an older person, his consideration of pulmonary tuberculosis should be as automatic as it would be if the story had been presented to him by a younger person.

Temperature. Of the charts reviewed, 51% showed an elevation of temperature of at least several days' duration during the course of the hospital stay. Many discrepancies can enter into the evaluation of fever in the elderly. The following are the commonest sources of error: the few times in a 24-hour period when the temperature is recorded, self-observation, and most important of all, the fact that the readings were oral, whereas accurate temperature observation in older persons can be obtained best by rectal thermometry. Banyai¹ felt that fever did not occur as often due to slower toxin absorption via narrowed lymphatics, poor stimulus and lessened irritability of the thermal center. Calmette⁴ found that chronic pulmonary tuberculosis in the aged was possible without fever. Ichok⁸ noted that febrile attacks were rare. Joress¹⁰ and Rubin,²¹ on the other hand, are inclined to the relative frequency rather than to the infrequency of this symptom.

Roentgen Study. Of the total number, 128 had Roentgen ray studies and in each the clinical opinion was confirmed. The distribution of the lesion from the report of the film was:

	Per cent.
Involvement of both upper lobes	45
Involvement of right upper lobe alone	17
Involvement of right lung and left upper lobe	11
Involvement of left lung and right upper lobe	7
Involvement of entire right lung	5
General involvement of both lungs	7
Miscellaneous other than above	8

Where the roentgenologist noted the type of lesion, a diagnosis of the fibroid form was made in 56%, one plate was read as miliary, and the remainder were grouped as fibro-ulcerative. In 60% cavitation was reported. Banyai¹ found 43.9% of moderately advanced and 52.5% of far advanced cases to have cavitation. Joress¹⁰

reported an incidence of cavitation by Roentgen ray reading in 43%. The corroborative value of the Roentgen ray in each of these patients is important because of the view expressed by Myers^{16a}; "our studies have led us to look on the Roentgen ray film of the chests of children as almost a total waste as far as tuberculosis is concerned." After this period of life, however, he urges the widespread use of Roentgen ray. In the old chest many changes may have occurred that will mislead, but on the whole the picture of pulmonary tuberculosis together with all other findings make a definite diagnosis.

Sputum. It is important in the control of tuberculosis to determine just how many elderly individuals with active lesions produce sputum which contains tubercle bacilli. In this series, the report was positive in 69%. No figures can be given as to how often during a period of years in which the patient had tuberculosis, known and unknown, the sputum was positive or negative. Undoubtedly spontaneous conversions occur, but when or how often cannot be said. It is unfortunate that, unless some check with periodic sputum examination is made, it cannot be known when elderly patients with the disease, 95% of whom cough and 87% of whom have expectoration, are dangerous to those with whom they live.

In Banyai's¹ group the sputum was positive in 79.1%. In Mcade's¹⁵ small series, the positive percentage was 61. Myers¹⁷ reported 56% in his list, and Joress¹⁰ 44%, with the note that "undoubtedly a greater incidence of positive sputum cases would have been found if other methods (besides the ordinary stained-smear examination) had been employed." Making a study of a large number of individuals in an old-age institution, not particularly suspected of any disease, Goldmann and Wolff⁶ found an incidence of 2% of positive sputum. A recent repetition of this work in Italy²⁵ found 3 cases positive in 198 persons in a home for the aged. On thoroughly studying these 3, they were found to have pulmonary tuberculosis with such a bland clinical complex as to justify the opinion that they were well. So much for the individual; the positive sputum is another matter. Certainly where the Roentgen ray is so frequently correct, and the sputum positive in 69%, a diagnosis should not be difficult.

Symptoms of Onset. As a guide to differential diagnosis, it should be noted in what manner the abnormal condition first presented itself to the patient.

In order of frequency the following symptoms of onset were recorded:

	Patients.
Cough	29
Common cold	23
Pleurisy	9
Weakness	8
Hemoptysis	6
Dyspnea	3
Nausea, night sweats, pneumonia, nervousness	each 2
Heart trouble, hiccoughs	each 1
No particular symptoms	20

For the most part, the onset appeared to be innocuous and diagnosis had to wait upon a continuation of such symptoms beyond any ordinary expected period of time, or for the development of more alarming complaints, or even for other cases in the family to occur to require investigation.

Tuberculin Test. We have no figures for the tuberculin test in this group. In the literature there are conflicting views. Kereszturi, Goldberger, and Nojima¹¹ performed the intradermal tuberculin test using 0.1 mg. O.T. on 353 white persons, age 40 to 92, and found that 96% were positive. These persons were similar to our group, namely, urban dwellers of the lower economical stratum. They concluded that "disappearance of tuberculin allergy with advancing age is rare." It might be predicted that with the general fall in the distribution of tuberculous infection the use of the tuberculin test in older persons will become increasingly important. Of course when clinical impressions and Roentgen ray readings are equivocal, the tuberculin test together with every other form of examination that may aid, must be used.^{7,12}

Diabetes Mellitus. It was found that 15 (11%) of this group had both pulmonary tuberculosis and diabetes mellitus. In Rubin's²¹ group the incidence was 17%. All of our diabetic patients had positive sputum. Twelve (80%) had a Roentgen diagnosis of cavitation. Since there is a greater incidence of cavitation (80% as compared with 60%) and of positive sputum (100% as compared with 69%) in the diabetics, it is indicated that these patients must be more carefully observed because the average elderly diabetic is usually a home-body, thus increasing the chance of spread of the pulmonary disease in the family. Certainly diabetes mellitus in older patients with tuberculosis increases the gravity of the case. In Jorress'¹⁰ group, where there was an incidence of 13.3% of diabetics among his tuberculous patients, 37% of the total mortality occurred in this fraction. In our series, death occurred in 52% of the 136, but among the diabetics the mortality was 60%.

Therapy. Of this group only 6 (4.4%) had more than bed or ambulatory hospital care. In 2 there were phrenic operations. In the remaining 4 pneumothorax was attempted, in 1 of whom it was completely successful, 1 developed marked hydropneumothorax, and in 2 it failed to be induced. It is generally felt that treatment too often is too conservative. However, the pthysiologist who does pneumothorax should follow the lead of those surgeons who are evaluating their older patients closely so that needed surgery can be done when indicated. This surgical attitude has been summarized by Mayo and Nettrour¹⁴: 1, careful evaluation of the condition and reserve of the patient; 2, individual preoperative planning, assuming sufficient skill to perform the task with the least risk; and, 3, careful attention to detail which, to the highest degree that can be obtained, is the secret of success in surgery of the aged. These postulates

are completely applicable to the case when pneumothorax is considered.

Discussion. Those who have studied pulmonary tuberculosis in the higher age group are impressed with the lack of emphasis on this phase in the study of the disease. A flank attack on this weak spot would circumvent more circuitous methods to the same end, namely, the lessening of the general incidence of tuberculosis. Jennings⁹ sums up the matter thus: "the prevalence of tuberculosis in the older age groups has not been stressed in proportion to the vital aspects of the situation as a public health problem." Drolet's⁵ warning that the incidence of the disease is falling without a proportional drop in mortality is not cheering. This mortality ratio has persisted in the face of increasingly radical procedures. The inference is that isolation, rest, and careful case control have stood the physician in better stead in handling the disease in gross than any method elaborated to handle the disease in individuals. A reduction in general morbidity means a lowering in general mortality. The older unrestrained and infectious members of society must be found and controlled to prevent their continuous contribution to the chain of tuberculous infection.

Isolation of the old positive-sputum patient, however, presents a gigantic problem. This responsibility is not strictly speaking that of the sanatoria because the aged tuberculous patient may not be amenable to active therapeutic measures, nor is he readily adaptable to a sanatorium regimen. A sympathetic public has never refused to support anything pertaining to child health, yet prevention of tuberculosis in children is so definitely associated with the isolation of the child's tuberculous progenitors that the measures in vogue at present are a generation tardy. Institutionalizing children from infected homes in preventoria and returning these same children to their homes without removing the source of the infection is not only epidemiologically futile but also harmful therapeutically. The removal of the old tuberculosis carrier from his home is as a matter of fact usually difficult, and may require the enactment of special state measures to effect its accomplishment.

The establishment of separate communities for old tuberculosis carriers close to large municipalities or on the grounds of the state sanatoria would be an interesting and not too costly experiment for one of the large states to undertake. After the initial outlay, the cost of maintenance plus the possible general lessened incidence of the disease would be less than the support of these patients in the more expensive general hospital, to say little of the benefits to the state of a falling tuberculosis rate. Prior to the withdrawal of such individuals from active communal life, each would be reviewed by those expert in the disease to render an opinion as to whether more active treatment could be given. Otherwise these homes would be limited to the older tuberculous patient for whom we as yet have no

procedure that will render him safe to his community. As compensation to the patients there would be comfortable homes, gardens, minor occupational therapy and association with those of their own age and times. The public would be served in having a reduction in the incidence of tuberculosis by the stoppage of a major source of the disease at its very origin.

Summary. In 3000 routine postmortem examinations done at the Philadelphia General Hospital, it was found that pulmonary tuberculosis was present in 25% of the patients. The older age group, 60 years and above, comprised one-third of the total necropsy figure, and in this fraction there was 28% of the total incidence of pulmonary tuberculosis. Included in this 28% were 11% of the fibro-ulcerative, 8% of the miliary, and 65% of the healed fibroid form of pulmonary tuberculosis.

If the tuberculosis figures could be applied to the general older age population, it would appear that in persons over 60, 5% have fibro-ulcerative, 0.5% have miliary, and 15% have healed fibroid pulmonary tuberculosis. A comparison by race showed that the active form of the disease was equally as common in elderly whites as in elderly negroes, that the miliary form was somewhat more common in the elderly negro, and that the fibroid form was much more common in the elderly white person.

The symptom complex is quite like that seen in younger persons, but may be obscured by the changes of increasing age, or be interpreted as due to senile debility. Cough and expectoration were the most common complaints, but hemorrhage, fever, and night sweats were not uncommon. As a rule, the symptoms of onset of the pulmonary condition were mild.

In a study of 136 hospital protocols of older persons who were in the tuberculosis division of the Philadelphia General Hospital, there was a positive family history in 26%. The Roentgen ray report confirmed the clinical impression in every case where it was used, and recorded cavitation in 60% of the patients. In 69% there was a positive sputum by the routine stained smear method. In the diabetics who composed 11% of this group, the sputum was positive in each case, and cavitation was reported in 80%.

Active therapy was negligible.

Conclusions. The fact that pulmonary tuberculosis is not uncommon in elderly persons seems to fail to impress both the public and the physician, possibly due to the nature of the older body affected by a chronically progressive disease. The actual incidence would indicate that this large group is a major obstructive feature in the national tuberculosis program of segregation of open cases. In brief, what is needed is earlier diagnosis, coupled with more stringent isolation and more active treatment. Such a program would tend to lessen the general incidence of the disease and also to do more for the older person so afflicted. Increased emphasis on the geriatric

factor in tuberculosis would benefit not only the older patient but the general population.

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V. HUMAN CONSTITUTION AND SYPHILITIC INFECTION.

A REVIEW OF THE LITERATURE, A PROJECTED METHOD OF STUDY, AND PRELIMINARY RESULTS IN 36 PATIENTS.*

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IN the several centuries preceding the development of serologic tests for syphilis and modern antisyphilitic treatment, it was generally assumed that every person infected with syphilis and untreated therefor ultimately developed some lesion of late syphilis. With the then existing lack of laboratory diagnosis, many infected patients were unrecognized as such; and in those recognized, the progress of the infection could be followed on a clinical basis only. Moreover, then as well as now, treatment for all patients recognized as syphilitic was the universal rule, and the course of the infection was more or less profoundly modified by this factor.

Not until 1929, with the publication of Bruusgaard's¹ important study, was any accurate information available concerning the spontaneous evolution of syphilitic infection in untreated persons.

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For the first time, it became clear that the course of syphilis was widely variable. In approximately equal proportions, in persons observed in the absence of treatment over many years, four general types of evolution of the disease were observed: 1, spontaneous "cure," *i. e.*, complete freedom from all detectable clinical, laboratory, and even necropsy evidence of the disease; 2, prolonged latency, *i. e.*, no clinical evidence of disease manifestations due to syphilis, but the persistence of laboratory evidence of infection manifested by positive serologic tests of the blood; 3, the development of apparent allergy, the sensitization of the patient to his own treponemes, and the explosive appearance of allergic gummatous benign late syphilis, involving chiefly skin, mucosæ, bones, and eye; and, 4, the very gradual evolution of the degenerative and potentially crippling or lethal late lesions of cardio-vascular or neurosyphilis.

Quite obviously, it would be of major importance in the individual management of syphilis, if not in its public health control, if the eventual course of syphilitic infection in each of these four directions could be anticipated in the patient at the moment of his infection. Both type and amount of treatment might be profoundly modified if one could predict that Patient A, just infected with syphilis, would succeed, even without treatment, in controlling his own infection completely, while Patient B was a candidate, even with standard treatment, for the eventual development of disabling or fatal syphilitic disease.

This study was planned as a study of certain factors which might influence the course of syphilitic infection in the individual patient.

Possible Reasons for Variations in the Course of Untreated Syphilitic Infection. We may consider three variables: 1, the infecting organism; 2, extraneous factors, such as intercurrent disease, nutritional deficiencies, pregnancy, and so on; and, 3, the defense mechanism of the host.

The Infecting Organism. There has been much clinical speculation and some experimentation as to whether variations in virulence of strains of *T. pallidum*, or variations in the size of the inoculum, might produce corresponding variations in the course of syphilis; but neither in human beings nor animals has any convincing proof of either of these hypotheses been adduced.

Aside from strain virulence *per se*, there is some clinical evidence suggesting the "tropism" of certain strains of treponemes for the nervous system of human beings. The suggestion has been made that there may be "neurotropic" and "dermotropic" strains; though tropism for other body tissues has not been even clinically identified. Unfortunately, it has not proved possible to confirm these reputed strain variations in the laboratory in a satisfactory manner.

Nevertheless, variation in strain of organism must be kept in mind as a possible, perhaps even probable; explanation of variation

in the course of the infection, though proof of the hypothesis must wait upon the so far unaccomplished successful cultivation on artificial media of virulent *T. pallida*.

Extraneous Factors. The influence of intercurrent disease, especially intercurrent infection, on the course of syphilitic infection cannot be accurately evaluated. In associated tuberculosis and syphilis, there is some evidence, not too convincing, of effect of one upon the other (Padget and Moore¹⁹); but in other associated diseases, there is only the vaguest speculation.

Only two extraneous factors can be implicated as even a probable influence on the course of syphilis: pregnancy and nutritional deficiency. It seems reasonably clear that in some as yet unidentified manner, pregnancy exercises a favorable influence on syphilitic infection (Moore^{15a,b} and Kemp¹²); and at least probable that nutritional deficiency, especially of vitamin A, B, or both, may predispose to the development of certain forms of neurosyphilis, especially tabes dorsalis (Moore and Woods¹⁷).

No extraneous factor can be suggested, however, to account for the variable course of untreated syphilis as observed in an entire syphilitic population.

The Defense Mechanism of the Host. It is quite clear to the student of infectious disease that human beings vary enormously in susceptibility to many of them, and in the severity of their manifestation. At one end of the distribution scale is a small group of "non-susceptibles," rarely if ever attacked by acute infections, and if so only mildly ill; at the other, an equally small group of "susceptibles," prone to many infections and seriously affected by all of them. The majority of the population stands midway between these two extremes.

The explanation for this epidemiologic phenomenon appears to lie within the individual and to be dependent on factors loosely embodied within the term "human constitution."

As applied to syphilitic infection, this inherent variability in human constitution does not extend, as with certain acute infections, to natural immunity against infection, since, so far as is known, all human beings are susceptible; but it seems the most likely explanation of the variable course of disease in infected persons.

The literature on the relationship of human constitution to disease is already vast and rapidly growing. No attempt will be made to review it in detail. We point out only that emphasis is shifting from the anthropologic and anthropometric approach of earlier workers (cf. especially Draper⁶) to a more purely biologic approach. To many workers, including ourselves, it seems probable that whatever the relationship between bodily habitus and degenerative or metabolic diseases may be, this relationship can hardly be as clear cut to infectious diseases, acute or chronic. Here the relationship must depend upon inherent biologic factors, such as, for example,

the variable ability of different persons to produce antibodies to organisms or antigens. There is as yet no clear cut evidence that "biologic constitution," if one may coin the phrase, is related to "physical constitution."

Even the literature on the relationship of human constitution to syphilitic infection is so large, so vague and diffuse as almost to defy adequate discussion. There are, for example, many studies, especially recently from our own clinic, which show quite clearly that race (Turner²⁵ and Zimmermann²⁶) and sex (Turner²⁵ and Moore^{15a,b}) profoundly modify the individual's reaction to *T. pallidum*. In many respects, from the predominating type of early tissue reaction to the relative incidence of such late manifestations as cardiovascular or parenchymatous neurosyphilis, syphilis differs in the Negro and white races. Both in experimental animals and human beings, syphilitic infection is milder in females than in males. These facts have been repeatedly observed, but as yet there are neither definite information nor adequate hypotheses as to why they should be so.

Excluding from further discussion these two factors of race and sex, the literature is fortunately summarized (discursively) in two monographs: to 1929, by Königstein and Wertheim,¹³ and to 1937 by Curtius, Schlotter, and Scholz.⁵ From them, the following discussion is drawn.

Certain clinical facts seem clearly agreed upon, and are related by most observers to "human constitution." There is no proof of "complete innate immunity" to syphilis in human beings, though such a suggestion is contained in the observation (Brandt³) that prostitutes who have not acquired the disease within the first 3 years of practice rarely do so later. There are frequently repeated combinations of several syphilitic symptoms (*e. g.*, the association of iritis, the folliculo-papular syphilide, and hydrarthrosis in Negroes with early syphilis) or of involvement of paired organs (cochlear nerve lesions). An extensive early tissue reaction (florid early secondary syphilis) seems to protect the patient against the subsequent development of parenchymatous neurosyphilis; while conversely, paresis and tabes tend to occur in those whose outward evidence of early tissue reaction was minimal or lacking. Likewise, benign late (allergic gummatous) syphilis rarely precedes or is associated with parenchymatous neurosyphilis. The disease is always more severe in floridity of early lesions and in incidence and extent of gummatous late lesions in "virgin soil," *e. g.*, a population into which it has just been introduced, than in a population in which it has been present for many years.

Hereditary factors have been studied; and there is some evidence, not very convincing, that "degenerative," *i. e.*, parenchymatous, neurosyphilis is more frequent in families in which other degenerative diseases of the nervous system tend to occur.

It has been repeatedly suggested, but never proved, that syphilis acquired at an advanced age is more serious than in early adult life.

Many attempts have been made to link body habitus with cardiovascular and neurosyphilis. Neusser¹³ thought that "hypoplastic" individuals are particularly disposed to the localization of syphilis in the aorta but according to J. Baucr² and to Bartel,¹ the "digestive" and "muscular" types are those particularly disposed to aortitis. While they used somewhat different classifications of habitus, Stern,²⁴ Hirschl-Marburg,¹¹ and Rasdolski²¹ are reported to be in essential agreement regarding the relation of habitus to paresis and tabes; they found that paretics tended to be hypersthenic and tabetics hyposthenic. Gyárfás,¹⁰ in a small series, reported reverse findings.

Königstein and Wertheim¹³ summarize some of their own investigations on constitution and syphilis. They state that their results are based on an investigation of 10,000 cases but give few specific data. They use the classification of habitus as normal tonic (sthenic), hypertonic (hypersthenic), hypotonic (hyposthenic) and occasionally use also the term asthenic. They believe that papular eruptions and leukoderma are most frequent among hyposthenics; alopecia is more frequent with hyposthenics and sthenics; recidive eruptions are most common with hypersthenics; malignant syphilis (report based on 36 cases) occurred oftenest with hyposthenics and next oftenest with hypersthenics. They also tried to correlate spinal fluid abnormalities in secondary syphilis with habitus but found no essential difference between the different body types. They do report that hyposthenics with papular exanthems had a definitely higher incidence of spinal fluid changes than did sthenics with the same type of eruption. They attempt a correlation of some manifestations of early syphilis with hair color and report that recidive eruptions and alopecia are more frequent with blonds than with brunettes, while the reverse holds true with leukoderma.

Königstein and Wertheim mention several observers who have found that the rapidity with which seroreversal occurs under treatment can be correlated with blood group. Persons belonging to group "O" become seronegative most rapidly; those belonging to group "A-B" most slowly.

Since 1929 a number of articles have been published dealing with constitution and syphilis, particularly in the European literature. Most of these contribute little to the subject but some are worthy of mention.

Reiter²² in 1929 carried out experiments to test the hypothesis that relative and absolute disposition to infectious diseases is based on certain constitutional metabolic peculiarities. He selected cholesterol metabolism as the factor to investigate and syphilis as one of the diseases. He conducted experiments on a limited number of human syphilitics and on a still more limited number of

rabbits. His conclusion was that the growth of *T. pallidum* is favored by high cholesterol content. However, he found what he considered to be evidence that the blood cholesterol of patients who had developed neurosyphilis (mostly paresis or tabes) were lower than the average. He extended his hypothesis to include this observation by assuming that in individuals with syphilis and low blood cholesterols, the conditions in the tissues generally are relatively unfavorable for *T. pallidum*, so the organisms seek out organs with high cholesterol content, in this case, brain and spinal cord. His recorded data are not at all convincing proof of his conclusions.

Dujardin⁷ first (1922) advanced the theory that the type of syphilis a patient might ultimately develop could be determined by intradermal test with horse serum (0.2 cc.). His theory was based on his doctrine of "hetero-allergy" and his belief that individuals who developed gummata were allergic and those who developed paresis and tabes were anergic. His doctrine of hetero-allergy was that an organism sensitized to one specific antigen is at the same time sensitized to other non-specific antigens. Accordingly, a patient who was about to develop gummatous syphilis would react intradermally with horse serum as well as with luetin, while the reverse would hold true with paresis and tabes. Sézary and Coumetou²³ in 1930 reviewed Dujardin's publications^{7,8a,b} and presented convincing evidence that neither the hypothesis nor the observations were correct.

Perkel and his associates²⁰ in 1930 inquired into conditions predisposing to the development of cardiovascular syphilis. They regarded inadequate treatment, particularly in the early stage, as the most important factor; but also believed that constitution (habitus and "underdevelopment and weakness of the cardiovascular system") and unfavorable influences in the environment were important. Of their patients with cardiovascular syphilis, 67.5% were of the pyknic habitus.

Lazarovits¹⁴ in 1932 reported on the rôle of constitution in the development of late syphilitic changes, particularly aortitis. He investigated 200 men and 100 women, supposedly selected only in the sense that they had had the disease for at least 10 years unless they had already developed late manifestations. He compared the outcome of the disease with habitus (Kretschmer's classification) and concluded that the pyknic type showed the most tendency to the development of aortitis.

Guirdham⁹ in 1936 investigated the body type of the general paralytic in 27 patients with paresis, using both Pignet's measurements and Pignet's index calculated from Kretschmer's average figures. He concluded that variations in weight in paresis were sufficient to change the classification. He also concluded that his data do not afford a basis for assuming that any one type is

predisposed to paresis, but does not preclude the possibility that paretics are relatively more pyknic than tabetics.

Curtius, Schlotter and Scholz⁵ carefully studied a group of 101 tabetics and their families, and by the same methods, a control series of 200 cases of non-tabetics and their families. They found that while there was no significant difference in the two groups as far as body type was concerned, there was a correlation between body type and the severity of tabes. Tabes tended to be more severe in the slender (asthenic) individual than in the more broadly built (hypersthenic) individual. That the asthenic habitus was not the result of tabes they attempt to show by early photographs of patients and by examination of their families. Tabetics more frequently had neurologic and psychiatric disorders antedating the development of their tabes, and their families a higher incidence of epilepsy, feeble-mindedness and psychoses than the control series. Tabes, and particularly "rudimentary" tabes, was commoner in the families of tabetics, while other forms of central nervous system syphilis were not. These authors investigated other factors, such as the vegetative nervous system, the arrangement of capillaries in the nail bed, endocrine glands, blood picture, blood type, allergy, and so on, without finding significant differences between the test and control groups. They do not consider the possible relationship between tabes and nutritional deficiency.

Method of Study. In spite of the vagueness of results achieved thus far, it seemed advisable to study the problem of the relation of constitution to the course of syphilis by a biologic rather than an anthropologic approach. To eliminate the factors of race and sex, whose effect on the course of syphilis is well known, the study was limited to white males who had developed the following types of syphilis: 1, late latent syphilis of 15 to 20 years' duration; 2, gummatous syphilis; 3, degenerative—fibrotic syphilis: (*a*, cardiovascular; *b*, tabes or paresis). The patients were also to have had no treatment—particularly in the early stage—or wholly inadequate treatment. Data gathered on them included a detailed history of the syphilitic infection, the number and severity of other infectious diseases they had experienced, active and passive immunization and allergy. Information was also secured on positive physical findings, necessary routine laboratory work (including routine serologic tests for syphilis, spinal fluid findings, Roentgen ray studies of heart and aorta) and special investigative laboratory data. These special data included quantitative Wassermann tests, results of revaccination with cowpox, luetin tests, blood group, horse serum sensitivity, Dick test, Schick test, and quantitative tuberculin test (clinical and roentgenologic evidence of tuberculosis being absent in all). In order to facilitate the gathering of data, special blanks with designated spaces for different data were printed and were filled out on

each patient studied in the investigation. (Copies of the recording blanks are available on request.)

As the study progressed it became apparent that the rigid criteria set up for the selection of material made it difficult to secure patients, particularly in a clinic whose clientele was predominantly Negro. The criteria were therefore relaxed somewhat to permit the selection of patients whose late latent syphilis was of only 10 years' duration; and patients with gummatous or degenerative late syphilis were selected even if they had had a good deal of treatment, provided it was administered late enough in the course of the infection not to have influenced the immune state to any great extent (*i. e.*, after the fourth year). In spite of these relaxations it was not possible to secure enough suitable patients in the period available for the study to provide real statistical significance.

Technical Details of Study. The Roentgen ray studies of heart and aorta included fluoroscopy and posterior-anterior and left anterior oblique teleroentgenograms. The quantitative Wassermann tests represent titered Eagle complement fixation tests. In the revaccination tests with cowpox, vaccinoid as well as vaccinia reactions were recorded as positive; the tests were done with the "multiple pressure technique." The luetin tests were performed with "organic luetin" furnished us by Dr. George W. Raiziss of the Dermatological Research Laboratory. Horse serum sensitivity was tested for intradermally by the injection of 0.1 cc. of 1 to 100 dilution and ophthalmically by the instillation of several drops of a 1 to 10 dilution of normal horse serum. The quantitative tuberculin tests were performed with recently prepared dilutions of "old tuberculin."

Results. The results of the study are presented in Tables 1 and 2. Data are presented on 7 patients with late latent syphilis, 10 patients with gummatous syphilis, and 19 patients with "degenerative-fibrotic" syphilis. Of the 19 patients in the latter category, 6 had tabes, 4 taboparesis, 6 paresis, and 3 had cardiovascular syphilis.

In Table 1 are summarized the data from the study of the patients relative to the frequency and severity of past infectious diseases and to allergy. No conclusions are permissible, though it is suggested that the severity and frequency of the acute infectious diseases are higher in patients with long-standing latent syphilis than in those with various late manifestations.

In Table 2 are summarized the results of the various tests for immunity done on the patients. As was to be expected, the incidence of positive luetin tests was highest in patients with gummatous syphilis; in contradiction of Dujardin,^{7,8a,b} there was no relation between skin sensitivity to luetin and to horse serum; in confirmation of Moore and Eagle,¹⁶ there was no relation between quantitative Wassermann titer and type or severity of disease. For the other observations enumerated, the number of cases reported is too small to justify conclusions.

Discussion. The purpose of this article is to emphasize a method of approach and to encourage others to attack the problem from

TABLE 1.—HISTORY OF INFECTIOUS DISEASES AND ALLERGY.

Type of syphilis.	No. of patients.	Average infectious "disease index."	Extremes of "disease indices."	Allergy in patient.	Allergy in family.
Late latent	7	13	9-18	1 definite 2 history urticaria on one occasion 1 history of eczema?	2
Gummatous	10	6	0-17	3 definite 1 history urticaria on one occasion	0
"Degenerative fibrotic" (cardiovascular, tabes, paresis)	19	7	0-18	1 definite 1 history migraine	1 definite 1 history migraine

In taking history of infectious diseases on each patient an attempt was made to estimate the severity of each disease by the 1, 2, 3, 4 grading system. "Disease index" was determined for each patient by the addition of severity indices of infectious diseases which patient had suffered.

In the 7 patients called "Late latent," the classification of 2 could be questioned. In 1 case, a lumbar puncture could not be obtained; in the second case the patient had been classified as "Late latent" but a subsequent examination revealed the residuum of a juxta-articular nodule and a history of 2 others which had disappeared with treatment.

In the "Gummatous" group, there was 1 patient in whom the history was unreliable, partly on account of language difficulty. If he is omitted there are 9 patients with disease index of 7.

In the "Degenerative-fibrotic" group, 8 of the 19 patients had histories of infectious diseases which were none too reliable. If they were omitted, there are 11 patients with an average "disease index" of 9. Also in this group, 9 of the patients with neurosyphilis had apparently had some arsenical treatment fairly early in the course of the disease which might have influenced them to develop at least a more serious type of neurosyphilis.

TABLE 2.—TESTS OF IMMUNITY.

Type of syphilis.	No. of cases.	Results of tests.								Wassermann titer.	
		Revaccination with cowpox.	Luetin test.	Blood group (Moss).	Horse serum sensitivity.	Dick test.	Schick test.	Quantitative tuberculin test.	Average.	Extremes.	
Late latent	7	4—pos.	3—pos.	3—II 2—III 1—IV (1 not tested)	1—pos.	1—pos.	2—pos. 1—pseudo	3—1:10 M 4—1: M	5	0-25	
Gummatous	10	7—pos.	6—pos. 1—? (KIT)	3—II 3—III 1—IV (3 not tested)	No pos.	4—pos.	3—pos. 1—comb.	4—1:10M 5—1: M 1—1:100	19	0-100	
"Degenerative fibrotic" (tabes, paresis, cardiovascular)	19	7—pos. (3 positives uncertain of previous vaccination) (1 not tested)	4—pos.	2—I 4—II 2—III 9—IV (2 not tested)	No pos. (3 not tested)	4—pos.	6—pos. 3—comb.	1—1:100M 8—1:10M 8—1: M 1—1: M neg. 1—100 neg.	19	0-150	

this angle. It is admitted that because of the rigid criteria for the selection of patients and the limited period of time available for the study, the number of patients here studied is not large enough to give statistical significance to differences in data.

The ultimate aim of such a study is the securing of data sufficient to enable one to predict the eventual outcome of infection in an individual with syphilis if he is untreated early in the course of his disease. This might allow real individualization of treatment. Patients with poor prognoses might be given more and perhaps different treatment than others, and other clues might enable the supplementing of ordinary methods of treatment.

In the patients of this study, the immunologic background to other diseases has been emphasized. Added desirable observations would be antibody production to bacterial (*e. g.*, typhoid vaccine) and foreign protein (*e. g.*, egg white) antigens. There are of course no present means of testing qualitatively and quantitatively for immunity against syphilis; and the mechanism of antisypilitic immunity may well not be comparable to that of most infectious diseases. The evidence so far available indicates that immunity in syphilis is predominantly tissue rather than humoral, and perhaps more comparable to immunity in tuberculosis than to that in acute infectious diseases. Possession of more knowledge of immunity in syphilis and ways to test for it would be invaluable and should facilitate to a great extent the study of constitution and syphilis, and the development of methods of prognostication.

Summary. The literature on the human constitution and syphilis has been briefly reviewed. A method of attack on this problem has been outlined and the potentialities emphasized. Data from cases studied in this manner have been presented.

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THE CEPHALIN FLOCCULATION TEST IN CIRRHOSIS OF THE LIVER.

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IN previous reports a flocculation reaction has been described which is usually positive in diseases characterized by diffuse inflammation of the liver parenchyma.^{1a,b} Details of the test have been described elsewhere. In brief, it consists of adding an emulsion of cephalin and cholesterol to diluted serum and noting the degree of flocculation and precipitation after 24 and 48 hours. The serum of normal subjects gives a negative test. Likewise, the sera of patients with disease of the bile ducts or chronic passive congestion of the liver usually give negative tests,* whereas cases of hepatitis (catarrhal jaundice) give positive reactions during the active stage of the disease.

It has already been indicated^{1a} that the test may be either positive or negative in cases with cirrhosis of the liver. It is inferred from studies on hepatitis that there may be concomitantly active injury to the liver cells in this disease. Cirrhosis, however, may be entirely quiescent; the scarring indicating a healing of some injury in the past. In such cases a positive flocculation would not be expected. With these assumptions in mind, the sera of a group of patients with cirrhosis of the liver were tested at various stages of their clinical disease.

For the past 4 years cirrhosis of the liver has been investigated by one of us (A. J. P.) at the Research Service of the First Medical Division at the Welfare Hospital, New York City. The beneficial

* A recent publication by Pohle and Stewart³ reports positive flocculation in many cases of chronic passive congestion of the liver and obstructive jaundice. The cephalin employed by these investigators was used directly after preparation and is obviously more sensitive than that used in the present studies. Our cephalin is aged in the air and sunlight for about 6 weeks until it becomes dark brown and gummy in consistency.

effects of a highly nutritious diet supplemented by vitamin B concentrates has already been reported² and more detailed analysis of these cases is now in preparation. In brief, the clinical progress in this cirrhosis group can be classified as follows:

1. *Favorable.* A significant number of patients show clinical improvement. This is characterized by gain in weight and strength, permitting the patient to resume his usual activity; by disappearance of ascites, edema, and jaundice without recurrence; by changes of serum proteins, bromsulfalein dye test, and Takata-Ara test towards normal values.

2. *Equivocal.* This group is composed of patients who show only partial clinical improvement for months or years. They do not recover robust health. Certain of these die apparently from "simple failure" of the liver. In other instances a fatal relapse is precipitated by intercurrent disease.

3. *Unfavorable.* Certain patients continue a progressive downhill course despite all forms of therapy.

We are reporting briefly a correlation of the cephalin flocculation reaction with the clinical course in a group of 40 selected cases of cirrhosis of the liver chiefly of the alcoholic type, some of whom have been followed 3 years or longer. Detailed descriptions of the clinical features are not included as they are to be presented by one of the authors elsewhere. Chemical data also are not reported here although the course of the disease was followed repeatedly with serum protein studies, bromsulfalein determinations, icteric index values and Takata-Ara reactions.

It has been impracticable to conduct the cephalin flocculation studies in a systematic manner in all instances. In certain cases the initial test was not performed until after a favorable trend had been established. In others only a single determination was made because of the rapid demise of the patient. In the majority, however, a test was made approximately every 3 months. Readings were strikingly consistent from time to time and any changes marking a trend in the reaction were usually gradual unless an acute episode intervened.

The 40 cases of hepatic cirrhosis are presented in Table 1, according to the type of the cephalin flocculation reaction: those with persistently strong reactions (++++ and +++); those with diminishing reactions over a course of months or years; those with persistently negative or weak reactions (neg. and +).

TABLE 1.—CORRELATION BETWEEN THE CEPHALIN FLOCCULATION REACTION AND THE CLINICAL COURSE OF 40 PATIENTS WITH CIRRHOSIS OF THE LIVER.

Intensity of flocculation reaction.	No. of cases.	Died.	Stationary or unfavorable course.	Favorable course.
Persistently strong	17	12	4	1
Progressively diminishing	12	3	0	9
Persistently weak or negative . . .	11	3	0	8

Twelve of the 17 cases with persistently strong reactions presented in Table 1 have died. Seven of these had a rapid downhill course. In 5 cases an initial improvement was poorly maintained, and it was followed by relapse with the return of ascites, jaundice, and ultimate death. Of the 5 living patients, 4 are doing poorly, whereas 1 appears to be in good health. The latter case is somewhat atypical, since the patient is a non-alcoholic, and since his cirrhosis is complicated by myxedema.

The outcome has been considerably more favorable among the 12 patients who have gradually developed weaker flocculation reactions. Many of this group, when first observed, were indistinguishable clinically from the more severe cases. However, their course after entry to the hospital was more favorable. Relapses seldom were observed. Although there were 3 deaths in this group, only one instance was directly attributable to cirrhosis of the liver. This patient, who had shown marked improvement, died from a massive hematemesis following an alcoholic spree of several weeks. In some instances the flocculation test changed along with the general clinical improvement, while in others there was a lag of 6 or more months before serologic differences were detected.

There are also listed 11 cases which had weak or negative flocculation tests persistently. Eight of these have had a favorable clinical course. In this group 3 showed marked improvement before the initial tests were done. It is possible that they would have shown positive tests at the onset, and might therefore have been classified with the preceding group.

However, 3 patients in this group have died. At autopsy, one showed moderate portal cirrhosis together with extensive portal and mesenteric vein thrombosis. There is suggestive evidence that the other 2 deaths were not due to liver failure. Unfortunately autopsies were not done. One of the patients in this group, apparently with typical cirrhosis, has shown an unusually sluggish recovery from liver failure. There remain, therefore, 4 instances in which a negative test possibly may have been misleading as an index of a quiescent disease process.

Initial tests (Table 2) on the sera of our patients show that there is no correlation between the flocculation reaction and the presence or absence of ascites. However, in the presence of jaundice and ascites, or of jaundice alone, the test is rarely, if ever, negative.

TABLE 2.—CORRELATION BETWEEN THE CEPHALIN FLOCCULATION REACTION AND SYMPTOMATOLOGY IN 40 PATIENTS WITH CIRRHOSIS OF THE LIVER.

	Total No. of cases.	Strongly positive, ++++, ++++.	Moderately positive, +++, +.	Weakly positive or negative, +.
Ascites and jaundice	14	7	7	..
Ascites alone	13	6	2	5
Jaundice alone	4	2	2	..
No jaundice, no ascites	9	2	2	5
	<hr/>	<hr/>	<hr/>	<hr/>
No. of cases	40	17	13	10

These findings are supported by many isolated observations on other patients with cirrhosis of the liver of the Laennec type. Negative reactions are occasionally encountered, however, in cases of biliary cirrhosis with jaundice where intrahepatic obstruction of the bile ducts is a feature.

Discussion. There are numerous tests that reveal changes in one or another function of the liver, but there are few that aid in gauging the severity of the disease process in terms of life expectancy. From the limited number of observations in this study, it appears that in patients with cirrhosis of the liver the prognosis is grave when the flocculation test is persistently positive. On the other hand, the change from a positive to a negative test in a patient may be regarded as a favorable prognostic sign. Although the data are too few to be conclusive they suggest that the flocculation test may be of value in prognosticating the course of this disease. It is hoped that further application of the test will define more clearly the limits of its usefulness.

We have observed that the diagnosis of cirrhosis must be made with reservations when the flocculation test is constantly negative. For example, a number of cases of presumptive cirrhosis because of ascites, have eventually proved to be Pick's disease, thrombosis of the portal vein or neoplasia of the peritoneum. In several instances, also with negative flocculation reactions, cases with esophageal or gastric varices have been observed in which no lesions in the liver were present at operation or autopsy. Hepatomegaly with negative flocculation reactions is commonly observed in alcoholic subjects. These cases are often mistaken for cirrhosis, but occasional biopsies indicate that the underlying lesion consists of fatty infiltration of liver cells rather than parenchymal disintegration with replacement by connective tissue. It is not yet determined whether cirrhosis is an end stage of these fatty changes or whether the fatty liver is especially subject to damage by unfavorable conditions that may coexist. Our observations with the cephalin flocculation test favor the latter view, for positive reactions seldom appear in cases of fatty liver unless inflammatory or acute degenerative changes are also present.

Conclusions. The cephalin flocculation test has been employed in 40 cases of cirrhosis of the liver that have been treated with a highly nutritious diet supplemented by vitamin B concentrate. A correlation has been made between the clinical course of these patients and the intensity of the reaction.

1. The ultimate prognosis in patients with Laennec's cirrhosis showing persistently strong positive reactions is not favorable, irrespective of apparent clinical improvement.

2. Progressive decrease in the intensity of the cephalin flocculation reaction often accompanies clinical improvement and a return

of blood proteins to normal values. Relapses in this group are relatively uncommon.

3. A negative reaction does not exclude the diagnosis of cirrhosis. However, patients with persistently negative tests tend to have a relatively favorable course.

4. The intensity of the flocculation reaction does not parallel the presence or absence of ascites in cases of cirrhosis of the liver. However, no cases of alcoholic cirrhosis with jaundice have been encountered giving a negative reaction.

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CAUSES OF PAINLESS GASTRO-DUODENAL HEMORRHAGE.

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HEMATEMESIS, melena or both, unattended by pain is a common enough observation. Recurrences are the rule, the hemorrhages come without warning and in the intervals symptoms referable to the gastro-intestinal tract are absent or trivial. The diagnosis of duodenal ulcer is conventionally made. As soon as the patient's condition warrants, a gastro-intestinal Roentgen ray examination is done and the usual findings are negative, or at best reveal a slight deformity of the duodenal cap. If such a deformity is reported, the diagnosis of duodenal ulcer is considered clinched. If the Roentgen ray is reported negative, the ulcer is regarded either as healed, or not sufficiently physically pronounced, or so situated that it escapes recording on the Roentgen ray film. Such a case constitutes one of the commonest of hospital records under the classification of "bleeding duodenal ulcer."

It is obvious that such a case may not be considered closed because there are many causes for painless gastro-duodenal hemorrhages aside from peptic ulcer. For this reason, we have reviewed all cases of painless gastro-duodenal hemorrhages that have come to autopsy in this hospital during the past 15 years, and those in which a sufficient resection was done to permit an anatomic diagnosis. We have

omitted cases where simple exploration was performed because exploration, no matter how painstaking, is a notoriously uncertain guide in respect to the discovery of a bleeding lesion. Cases with a loss only of occult blood have been excluded; only those that presented a considerable hematemesis or melena, associated with an appreciable anemia and clinical symptoms of hemorrhage (dizziness, fainting, fall in blood pressure), have been accepted. Moreover, lesions of the jejunum, ileum and colon have not been considered.

There were left a total of 14 cases. A brief report of each follows.

Case Abstracts. CASE 1 (Path. 6253). Female, aged 68. Fever, chills and prostration 2 weeks. On one occasion had blood in stool. *Clinical diagnosis:* sepsis, perinephric abscess and pyelonephritis; right ureter obstructed. Operation: pyelotomy. On 7th day patient vomited. Gastric lavage showed old blood.

Autopsy. Purulent pyelonephritis. Thrombophlebitis of renal vein extending into inferior vena cava. Multiple emboli of branches of pulmonary artery with multiple hemorrhagic infarcts. Emphysema. Chronic mitral disease. Multiple erosions of the stomach with old blood in the lumen.

Summary. A case of sepsis following renal infection. The painless hematemesis arose from multiple erosions of the stomach.

CASE 2 (Path. 7583). Male, aged 46. A case of familial hereditary telangiectasis. Umbilical pain after meals. Aspiration of stomach showed old blood. Four years later an enlarged spleen and gastric retention of blood. On last admission, history of dizziness, faintness and black stools dating 3 days previously.

Autopsy. Chronic thrombotic obliteration of portal, splenic, mesenteric and left renal veins. Multiple peritoneal adhesions. Dilation of esophageal and gastric veins; healed ulcer of duodenum.

Summary. A case of multiple hereditary telangiectasis; healed ulcer of duodenum; portal obstruction of unknown etiology. The painless melena is due to portal obstruction.

CASE 3 (Path. 5951). Female, aged 24. History of probable gastric neoplasm. A few days before death, severe hematemesis is followed by severe anemia.

Autopsy. Generalized lymphosarcomatosis, hemorrhage arose from ulceration of a gastric tumor.

Summary. Lymphosarcoma; hematemesis from a gastric tumor.

CASE 4 (Path. 6516). Case of aplastic anemia with purpura; hemorrhages from nose and throat; hematemesis.

Autopsy. Aplastic anemia; hemorrhages in kidney, stomach, lung and endocardium.

Summary. Aplastic anemia.

CASE 5 (Path. 6720). Male, aged 48. Seven years belching and regurgitation of food; no pain. Two years occasional attacks of dizziness; 6 weeks attacks of dizziness, increasing pallor, weakness. Hemoglobin 32%; stools guaiac positive, 4+. Transfusion of 500 cc. of blood. Roentgen ray revealed an irregular bulb and a small pocket on the greater curvature of the duodenal bulb near the base. Partial gastrectomy. Resected specimen showed an ulcer on the superior wall of the first portion of the duodenum; gastritis with 6 erosions varying from 4 to 10 mm. in size not involving the submucosa.

Summary. Bleeding arose from ulcer of duodenum, gastritis and erosions.

CASE 6 (Path. 7101). Male, aged 37. Swollen abdomen 2½ months. Enlarged liver, jaundice, cholemia. On day of death, hematemesis.

Autopsy. Endophlebitis obliterans of hepatic veins, gastric erosions.

CASE 7 (Path. 7132). Female, aged 64. History of spells of vomiting for years. Following operation for cataract, developed uncontrollable vomiting with dehydration, azotemia and acidosis. Vomited large amount of bright red blood.

Autopsy. Pyonephrosis; healed duodenal ulcer; neoplasm of sigmoid.

Summary. Cause of bleeding?

CASE 8 (Path. 8258). Male, aged 50. Twelve years ago and again 3 years later hematemesis and melena with fainting. Well up to 3 days ago when there was sudden onset of melena and fainting. Hemoglobin 34%, despite several transfusions. On day of death, fainting, shock.

Autopsy. Multiple fresh erosions and hyperplastic gastritis. Healed peptic ulcer.

Summary. Healed peptic ulcer; gastro-intestinal hemorrhage from fresh gastric erosions and gastritis.

CASE 9 (Path. 8993). Male, aged 60. Anorexia, dizziness 3 days; hematemesis of a pint of blood and clots, later another large hematemesis. Blood pressure 80—50. Liver and spleen not palpable; died in coma.

Autopsy. Laennec's cirrhosis.

Summary. Hematemesis due to Laennec's cirrhosis of the liver with rupture of an esophageal varix.

CASE 10 (Path. 9761). Male, aged 59. Two years ago, marsupialization of pseudocyst of pancreas. Vomited black liquid 10 days ago. Blood pressure 80—60; severe anemia; 3 transfusions. Signs of myocardial failure and marked cyanosis; thrombosed veins of legs. Electrocardiogram showed poor myocardial function.

Autopsy. Chronic peptic ulcer of first portion of duodenum; severe coronary sclerosis; myomalacia of left ventricle; chronic esophagitis and gastritis at cardio-esophageal junction.

Summary. Painless gastro-intestinal hemorrhage from chronic peptic ulcer of duodenum; coronary sclerosis, and myomalacia of left ventricle.

CASE 11 (Path. 5477). In 1927, attack of abdominal cramps followed by melena. Remained well on dairy diet for 1½ years. Five hours before admission to the hospital had nausea, weakness, faintness and hematemesis of 2 full cups of blood. Hemoglobin slowly came down to 66%. Roentgen ray showed irregular contraction at midportion of duodenum. One week later partial gastrectomy. Duodenum shows very small areas of denuded mucous membrane with moderate infiltration of neutrophils and eosinophils and histiocytes with beginning fibrosis; moderate infiltration with mononuclear cells around Brunner glands.

Diagnosis. Duodenitis; probable healed ulcer. Five years later the patient feels perfectly well.

Summary. Painless gastro-intestinal hemorrhage from small duodenal ulcer.

CASE 12 (Path. 66848). Male, aged 21. Family history reveals one brother had a perforated duodenal ulcer; the other brother had "duodenal ulcer with bleeding." One week ago had melena followed by pallor and asthenia. Roentgen ray shows only an irritable bulb. Four years later reports to hospital that he has had 6 attacks of melena. Hemoglobin 68%. At this time Roentgen ray shows irregular deformity of duodenal bulb. Operation, 1 month later, partial gastrectomy; no ulcer found.

Pathologic Diagnosis. Chronic gastro-duodenitis.

Summary. Repeated melena without pain; no ulcer, only gastro-duodenitis.

CASE 13 (Path. 32749). Male, aged 37. In 1926, hematemesis 5 days before admission. Hemoglobin 25%, with 2 transfusions rose to 46%.

Roentgen ray negative. Partial gastrectomy; 2 small superficial erosions in resected portions of stomach. Ten years later, patient perfectly well.

Summary. Melena from gastric erosions.

CASE 14 (Path. 263625). Male, aged 55. In 1926, patient admitted with a history of intermittent attacks of vomiting of coffee-ground material associated with tarry stools, followed by weakness; no pain. Roentgen ray performed at another hospital 1 year previously revealed "ulcer." Roentgen ray soon after admission showed irregular duodenal bulb. Partial gastrectomy showed chronic duodenal ulcer. Fourteen years later, patient is well.

Summary. Painless duodenal ulcer with melena and hematemesis.

Classifying these 14 cases of painless gastro-intestinal hemorrhage, we find the following as causes of the hemorrhages:

TABLE 1.—CAUSES OF THE GASTRO-DUODENAL HEMORRHAGE.

1. Chronic peptic ulcer—3 cases.
2. Gastro-duodenal erosions—2 cases.
3. Erosions with healed peptic ulcer—2 cases.
4. Gastro-duodenitis—1 case.
5. Healed duodenal ulcer, no cause for bleeding found—1 case.
6. Thrombosis of portal vein—1 case.
7. Cirrhosis of liver—1 case.
8. Lymphosarcomatosis of stomach—1 case.
9. Aplastic anemia with purpura—1 case.
10. Endophlebitis of hepatic veins and erosions—1 case.

These proportions are by no means accurate as far as the incidence of painless gastro-duodenal hemorrhage is concerned, as these cases represent only patients who have been admitted to the surgical wards.

There were 5 cases of gastro-duodenal erosions, 2 in association with healed peptic ulcer and 2 without, and 1 associated with endophlebitis of the hepatic veins. If we include the case of gastro-duodenitis without erosion, we find that gastro-duodenitis with or without erosions is by far the most common cause of painless gastro-duodenal bleeding in our series. By an erosion, we refer to a loss of mucous membrane with necrosis and infiltration of the mucosa with neurophils and histiocytes. Healing, as a rule, leaves no scar. The erosion does not penetrate through the submucosa. An erosion corresponds to what is sometimes termed "acute peptic ulcer" or "Dieulafoy's ulcer." It is practically always associated with a gastritis or a duodenitis, or both.

The genetic relation of peptic erosions to true peptic ulcers is at present a much debated matter, aroused by Konjetsny's⁹ views, who holds that the genesis of ulcer is a gastritis or a duodenitis with the secondary formation of erosions.

The frequent anatomic association of erosions and peptic ulcer certainly suggests such a sequence. On the other hand, such a relation cannot be accepted unreservedly, and for the following reasons:

1. We have taken particular pains to note that in most patients who have the clinical earmarks of an erosion with painless melena

or hematemesis, the characteristic psyche which precedes the onset of the ulcer for many years is entirely missing. One of us (Moschcowitz¹¹) has described this type previously. Briefly, patients with peptic ulcer are intolerant, aggressive, "all or nothing" folk who have strong leanings to masochism and sadism. On the contrary, patients with clinical evidences of erosion are often calm, placid and phlegmatic. Nor have they the physical constitution of patients with peptic ulcer, as described by Draper.⁴ They have not the "lean and hungry" look of Cassius, the wide angled jaws, the prominent masseters and facial lines, the hard and tense expression, or the tendency to erythremia. The importance of constitution in the genesis of peptic ulcer is steadily gaining in recognition so that at present peptic ulcer is viewed by many students of the problem as a true psychosomatic disease. Indeed, we regard the determination or absence of this constitution as a vital link in the diagnosis of suspected ulcer.

2. Erosions are frequently found at autopsy as surprise findings, unassociated with ulcer and without having given rise to the slightest clinical phenomena. Such erosions are especially observed in prolonged sepsis. The possibility that, given time, such erosions may eventually develop into ulcer cannot be excluded.

3. Experimentally, erosions can be produced, though with difficulty, by ligation or by embolization of the gastric vessels. Furthermore, erosions are seen not uncommonly in the human stomach, accompanied by local arteriosclerosis. These erosions invariably heal within a short time without ever giving rise to the characteristic callous ulcer. Indeed, if it is eventually proven that an erosion becomes an ulcer, then the major problem is to discover the cause for the chronicity. Various investigators have succeeded in producing a chronic ulcer but by means that do not obtain in the human organism; for instance, by injecting chemicals in the neighborhood of the experimental ulcer, by repeated Roentgen ray applications, and so on.

Recently, Penner and Bernheim^{13a,b,c} have made significant observations that throw light upon the genesis of certain types of gastrointestinal erosions. The not uncommon autopsy findings of post-operative ulcerative and membranous enterocolitis led Penner and Bernheim to investigate the cause of these lesions. In reviewing the histories of 20 such cases in this hospital, they found that invariably death was preceded by the clinical picture of shock. In a later publication^{13b} they report 4 cases of acute ulcerative lesions of the esophagus and stomach which appeared post-operatively or subsequent to diabetic acidosis. In both the intestinal and gastric lesions, the changes are the same. "The earliest changes are observed in the mucosa where vascular congestion and subsequent focal hemorrhage, initially more prominent toward the base of the glands near the muscularis mucosa, are seen. Widening of the interglandular

stroma is observed, and the presence of mucosal edema. Focal mucosa necroses appear, unaccompanied by any significant cellular reaction. More extensive necroses may penetrate the deeper layers of the wall and be accompanied by an inflammatory cellular reaction. With the early or superficial lesions, the submucosa, muscularis and serosal layer may be without recognizable changes." They ascribe these lesions to the vaso-constriction conventionally recognized as the result of shock. Penner and Bernheim^{13a,b,c} submit experimental substantiation of this hypothesis by the reproduction of identical lesions in the gastro-intestinal tract in various animals by repeated intraperitoneal injections of adrenalin which caused prolonged shock.

Penner and Bernheim believe that their observations explain the cases reported by Eiselsberg⁵ of post-operative gastro-duodenal bleeding, which he believed was due to retrograde embolism; the majority of the cases reported by Cushing² of gastric erosions, which he ascribed as neurogenic in origin due to lesions of the inter-brain or its various pathways; and the acute erosions of the stomach and duodenum occasionally noted in severe burns and prolonged exposure to cold.

It would be hazardous to apply Penner and Bernheim's observations to the genesis of all gastro-duodenal erosions. Clinically, certainly, shock follows and does not precede the onset of uncomplicated erosions in our reported series. The solution of the problem hangs upon whether prolonged vaso-constriction in the intestinal tract may be the result of another mechanism beside shock. In any event, Penner and Bernheim's investigation may help to explain the association of erosions with bleeding peptic ulcers in our series.

Even if eventually accepted, Konjetsny's views concerning the pathogenesis of peptic ulcer explain only part of the mechanism but they by no means explain the primary etiology of peptic ulcer, for the reason that the cause of the gastritis or duodenitis still awaits a satisfactory solution. Konjetsny's belief that the gastro-duodenitis is the result of a toxic or infectious process has not received general acceptance; certainly it is not in accord with the known constitutional and neurogenic background of peptic ulcer, nor to its distinctive localization, the incidence of the disease in regard to sex and age, and the tendency to recurrence.

Of course it is conceivable that a true peptic ulcer with all its potentialities as a focus of infection may, in some instances, give rise to a gastro-duodenitis and thus pave the way for an erosion. Witness, for instance, the not uncommon association of ulcerating gastric carcinoma and erosion. In other words, an erosion of the stomach may be the result as well as the precursor of a peptic ulcer.

All in all, in the light of our current knowledge, it is impossible to insist upon a unitary etiology and biology of gastro-duodenal erosion and its genetic relation to callous peptic ulcer. A splendid

opportunity for such an investigation is offered by repeated gastroscopy in a suitable patient. As far as we are aware, the complete life cycle of a peptic ulcer has not yet been demonstrated by a gastroscopy.

Clinically, we can assert that erosions may have a different clinical picture and course from that of the callous peptic ulcer.

Two of the painless gastro-duodenal hemorrhages in our series were caused by chronic peptic ulcer. Eusterman⁶ reports that hemorrhage was the sole symptom of benign or inflammatory lesions of the duodenum in 1.5% of 1089 cases. The reason why some peptic ulcers are painless is not clear. Crohn¹ believes that the absence of pain is due to lack of sensitivity. In his patients with peptic ulcer, complicated by hemorrhage, employing the Libman test, he found that in 40.8% the patient was insensitive as compared to 12% in normal individuals. As this test is entirely a subjective one, one need be circumspect in its interpretation. In any event, it does not account for the *absence of pain in the remaining 60%* of sensitive individuals. Surely, pain in peptic ulcer is conditioned by factors other than the sensitivity of the individual. While there is still no agreement as to the cause of pain in peptic ulcer, Palmer and Heinz¹² submit convincing evidence that the pain is conditioned primarily by the acid content of the stomach, and that it is not directly due to pylorospasm, gastric mobility, or increased intra-gastric pressure, although these factors may be contributory. The size of the lesion has no bearing. Continuous neutralization of the acid slowly desensitizes the ulcer.

In how far these factors may apply to the explanation of the frequent absence of pain in pure erosions of the stomach unassociated with peptic ulcer cannot as yet be definitely ascertained. The superficiality of the lesions in erosions may serve in part as the explanation of the absence of pain, but more detailed studies of the above factors are necessary.

The one case in our series, where no cause for the bleeding could be found although a completely healed duodenal ulcer was present is similar to that reported by Reichard.¹⁴ A non-demonstrable cause for bleeding has been reported not infrequently. Such cases were termed by Hale-White⁸ "parenchymatous bleeding." Czyhlarz,³ Kuttner,¹⁰ Reichard,¹⁴ Ewald.⁷ These have also been reported in cholemia (deficient prothrombin and vitamin K) and in vicarious menstruation. Dr. M. A. Kugel has told us of another case of severe painless hematemesis and melena in which a subtotal gastrectomy was performed; no cause for the hemorrhage was found in the resected specimen. Unfortunately, the record of this case is lost.

The other causes of painless gastro-duodenal hemorrhage in our series require no comment.

Conclusion. Painless gastro-duodenal bleeding is usually the result of erosions and duodenitis; less frequent are true callous peptic ulcers. In one of our 14 cases no cause could be found. In painless gastro-duodenal hemorrhage where Roentgen ray evidences of peptic ulcer are absent or inconclusive, further study of the patient is obligatory to determine the cause of the bleeding. The genetic relation of gastro-duodenal erosions to peptic ulcer is discussed. In the light of our current knowledge it is impossible to insist upon a unitary origin of gastric erosion or upon its invariable genetic relation to callous peptic ulcer.

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AN APPRAISAL OF THE MEDICAL VERSUS THE SURGICAL TREATMENT OF IDIOPATHIC ULCERATIVE COLITIS.

FOLLOW-UP DATA ON FIFTY CASES.*

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ULCERATIVE colitis presents a number of fundamental problems that are as yet unsolved. The wide variety of therapeutic measures now employed in this disease and the frequency of unsatisfactory results attest to the present deficiencies in our knowledge. Opinion is divided first on the question of the specific bacterial nature of the disease. Those who deny a known bacterial etiology also doubt the efficacy of so-called specific vaccines and sera, and rely solely on a number of non-specific therapeutic measures. The second division of opinion concerns the place of surgery in treatment of the disease.

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The position taken in this matter depends in large measure upon one's opinion of the efficacy of non-surgical measures. For example, in the Mayo Clinic since the advent of "specific" therapy the number of cases treated surgically has progressively declined from 20% in the period from 1919-1923 to 1.4% in the period from 1932-1936.² On the other hand, those who have had less favorable experience with medical treatment employ ileostomy and analogous procedures in as high as 65% of patients with the disease.⁷ Such divergence of opinion emphasizes the need of obtaining all possible data that bear on this controversial question. The present study, therefore, was made to determine whether medical treatment alone was superior to combined medical and surgical therapy in a group of patients with ulcerative colitis observed during the past 12 years in this hospital. The follow-up analysis indicates clearly that those patients in whom one of various side-tracking operations was carried out are in better physical condition and lead more nearly normal lives than those treated medically.

Method of Study. Two groups of patients have been selected from ward* and private practice. One group, 23 in number, consists of those treated by medical measures only; the other group of 27 were first treated by the usual medical measures and subsequently by one of various surgical procedures. Only the more severely ill patients, with protracted diarrhea, melena, fever and anemia are included in the medical group, while those with milder forms of the disease which are known to improve spontaneously, are excluded from the study. This was done in an effort to make the two groups as comparable as possible. Even so, those treated surgically taken as a whole, were more seriously ill, for surgery usually was employed only as a last resort. In other respects, however, such as age, sex, duration of illness and geographical location, the two groups are comparable. Seventy-five per cent of the patients were personally known to one or both of us. The diagnosis in every case was made after thorough clinical study which included repeated proctoscopic examination, at which time cultures were obtained from typical ulcers, microscopic and bacteriologic study of the stools and Roentgen examination after a barium enema. Evaluation of the results of therapy was determined after personal interviews and examinations, or, when this was impossible, by means of questionnaires sent to the patients and by communication with physicians now in charge of them. In two instances interviews were made by a hospital social service worker. In every case certain specific questions were answered, so that the data are uniform in content. Without exception the information obtained was considered by us to be adequate to permit an accurate evaluation of the patient's status.

Results. *The Medical Group.* This group consisted of 23 individuals, of whom 14 survived, 8 died of the disease and 1 of unrelated causes, giving a mortality of 34%. The 14 survivors included 5 men and 9 women. In these observations, made from 1 to 12 years after the final discharge from this hospital, an effort was made to obtain both subjective and objective evidence of their subsequent physical status. A clear picture of the usual course of the disease and the

* We are indebted to Drs. E. L. Eliason and I. S. Ravdin for the privilege of studying patients treated on their surgical services.

ultimate prognosis for the average patient treated solely by medical measures is the first requisite in deciding for or against surgical treatment.

Twelve patients, 85% of those who survived, had had diarrhea either continually (5 cases) or intermittently (7 cases) since the illness had begun, on the average, 6 years earlier. Blood repeatedly appeared in the stools of two-thirds of the group, pus in one-quarter and mucus in three-quarters. They had on the average 6 bowel movements daily (1 to 14). Only 2 patients were free of symptoms of colitis, one of whom was a total invalid because of a complicating generalized arthritis. Although the group averaged 28 pounds above the minimum weight during their illness they were approximately 10% below their usual weight. One-half of them had had to return to hospitals because of recurrences of the disease. Three were complete invalids who should have been in hospitals. All were under constant medical supervision.

It seemed to us important to learn the opinion that each patient had concerning his own health. To the question "Do you consider yourself cured of the disease?" they unanimously gave a negative reply. Not one considered himself in excellent health, only 1 regarded her health as good, 9 as fair, 1 as poor, and 3 were invalids. With respect to productiveness, 5 were totally unable to do any kind of work, 5 were capable of light work, and 4 could do medium-heavy work during remissions of the disease. All were therefore either partially or wholly dependent financially.

Of the 8 fatal cases, 4 died after discharge from the hospital. While exact details of the immediate causes of death are not available, it is known that all had continuation of symptoms and ultimately died as a result of ulcerative colitis. The remaining 4 patients died in the hospital, 1 had extensive amyloid disease and died of renal failure, 2 developed perforation of the colon with peritonitis, and 1 with hypoproteinemic edema and anemia died suddenly at night without known cause.

Surgical Group. This consisted of 27 individuals, 14 males and 13 females. Seven of the group died, giving a mortality of 26%. The causes of death, which are discussed later, were as follows: 2 cases developed high intestinal obstruction and 1 adynamic ileus early in the post-operative period, 1 man committed suicide 3 weeks after operation, another made a highly satisfactory response to ileostomy but developed multiple liver abscess 2 years later. One man died in a state of severe malnutrition, hypochloremia and dehydration soon after ileostomy. In the final case, death occurred in another hospital following repair of a prolapsed ileum.

Ileostomy alone was performed in 12 instances, ileostomy with partial colectomy in 9, colostomy in 4, appendicostomy in 1, ileocolostomy in 1. The technical surgical aspects of 17 out of 20 cases are regarded as satisfactory. Three were, in our opinion,

inadequately treated by appendicostomy, cecostomy and sigmoidostomy which failed to divert the fecal current. The results in these instances, while not satisfactory, are nevertheless included in the consideration of the group as a whole.

Without exception the 20 patients who survived operation are greatly improved in health. The average gain in weight following operation was 38.5 pounds, the greatest gain was 100 pounds, the least 15 pounds. In no case did fever continue except in the 3 inadequately treated, in whom the disease recurred, with intermittent fever and melena. The red blood cell counts uniformly returned toward or actually to normal. Seventy per cent of the entire group led what they themselves described as a normal life, indicating that the limitations imposed by the operative fecal fistula did not constitute a significant handicap. Violent physical exertion was not possible, but mild athletic exercise was entirely feasible. One man was able to resume his occupation as a construction engineer, operating a hoisting crane.

Thirty per cent of the group were not able to return to an entirely normal life. Three laborers were unable to resume their previous occupations which involved heavy lifting and other strenuous exercise. Their disability was attributable to the nature of their occupations rather than to their physical condition, which was good enough to permit light work. Two others of the group, who were inadequately treated in one instance by appendicostomy and in the other by sigmoidostomy for a ruptured colon with a pelvic abscess, did not make complete recoveries. This must be ascribed to the inadequacy of the operations rather than to failure of surgical treatment. One woman, with coincident pulmonary tuberculosis, led a restricted life on that account although she had made great improvement following ileostomy. We believe it fair, in summarizing this group of 6 patients, to say that every one was definitely improved following operation and that failure to return to an entirely normal life was due either to inadequate surgical treatment or to circumstances unrelated to treatment.

We desired to obtain the patients' own opinion of the results of operation, for in advising surgical treatment the physician must consider the possibility of serious psychologic damage by an operation which may profoundly alter one's outlook on life. We were therefore especially interested in the answers to three questions. "Do you consider your present health better or worse than it was before operation?" The reply was unanimous, every patient considered his health improved. "Do you consider yourself better off with an artificial opening than you were without it?" All but one replied in the affirmative, that is, an artificial opening was not considered too high a price to pay for the improvement in health which resulted. "If you had to make the decision again would you be in favor of or against operation?" Eighteen out of 20 answered in

the affirmative, the remaining 2 expressed certain qualifications. The most decided were those of a 20-year-old single girl who, though she felt that operation had saved her life, regarded as intolerable the inconveniences, embarrassment and restrictions which it imposed upon her, and was flatly of the opinion that life would be unbearable with a permanent ileostomy. Hers was the only case in which the ileostomy fortunately proved to be temporary. She is now in normal health. Her objections are not, therefore, to the final result, but to the means of bringing it about. One other patient who had not improved following appendicostomy was doubtful of its efficacy. This is entirely understandable, since this inadequate procedure had resulted in most of the disadvantages and none of the benefits of surgical treatment.

Of the 7 individuals who died only 3 had had time to gain a definite opinion of the results of operation. One was entirely satisfied, he had resumed his work and for 2 years, before the development of avoidable complications, had been completely rehabilitated. Another committed suicide 3 weeks after ileostomy. While he was definitely psychotic it must be presumed that dissatisfaction with his operation precipitated his suicide. A third man, also a psychiatric problem, definitely improved in health for 5 years after ileostomy, but regarded it as a failure. He ultimately died after surgical repair of a hernia of the ileum because of his refusal to eat. Thus, of the 23 patients who expressed opinions, 19 were entirely satisfied, 2 were partially and 2 wholly dissatisfied with the results of surgical treatment.

The discussion of certain details of surgical treatment should be prefaced by the statement that we share the opinion of Cave and Mackie,⁵ Cattell³ and others that the operation of choice is one which produces complete diversion of the fecal current at a point just proximal to the diseased portion of the bowel. In the great majority of instances this has required an ileostomy. At a subsequent time, depending upon the patient's response to the preliminary procedure, removal of the diseased colon, preferably in 3 stages, should be carried out. This general plan has been deviated from in certain instances. For example, 6 patients who had an ileostomy and nothing more have made dramatic recoveries and have maintained good health for an average of practically 3 years. Under these circumstances we think it justifiable to withhold colectomy until clear-cut indications for it appear, with the understanding that if good health does not continue operation is advisable.

In 9 cases partial or complete colectomy followed ileostomy for the various reasons: 4 did not make what we regarded as satisfactory recovery after the preliminary operation, another had serious and repeated hemorrhages from the colon, necessitating its removal, 2 developed generalized arthritis which disappeared promptly after colectomy, 1 had a carcinoma of the colon which was removed during

the original operation. In general, we believe colectomy clearly indicated unless ileostomy results in complete return to normal health, with disappearance of bloody or purulent rectal discharges, and all systemic signs of infection such as fever and leukocytosis.

It is wholly unjustifiable, in the light of both our experience and that of others to regard any side-tracking operation in this disease as a temporary measure carrying with it a reasonable expectation that the normal fecal current may ultimately be reestablished. As

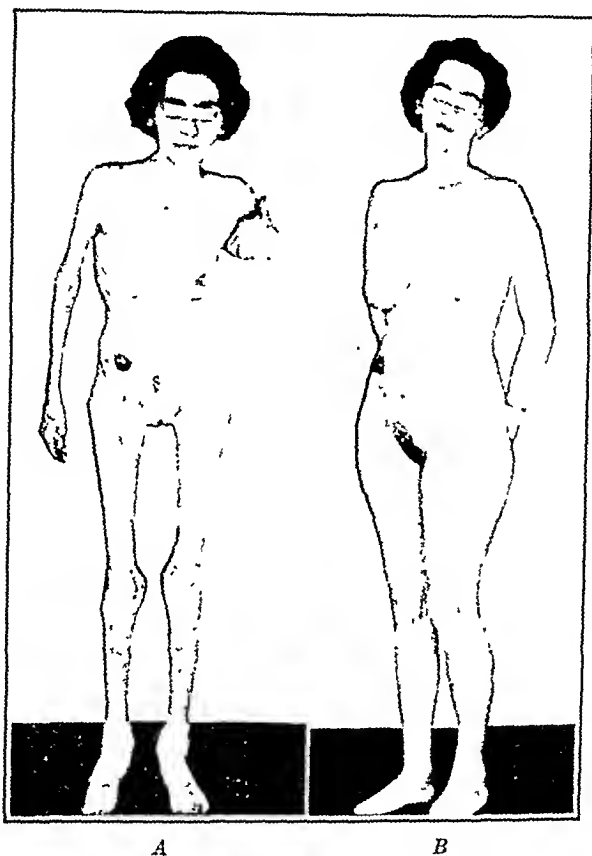


FIG. 1.—A, Patient E. L. 3 weeks after ileostomy and partial colectomy. B, The same patient 1 year later.

mentioned earlier, in only one instance in our series was it possible surgically to close the ileostomy. The success in this case depended upon the fact that the atypical, segmental disease process, restricted chiefly to the transverse colon, cleared up in a year after ileostomy, leaving the rest of the colon essentially undamaged. After partial closure of the stoma the colon returned to its normal configuration and caliber, judged by Roentgen examination, and 2 months later, in the absence of any signs of recurring disease of the colon, complete closure of the ileostomy was possible. The patient

has remained in entirely normal health for 10 months following this procedure. However, this fortunate outcome is so exceptional that it does not constitute grounds for offering what, in the great majority of cases, will prove a false hope which only delays the successful readjustment of the patient to a sometimes difficult situation.

Complications. It is not surprising that the post-operative complications were high in a group of patients in desperately bad condition before operation. The existence of multiple vitamin deficiencies accompanied by severe anorexia made proper caloric intake difficult. Anemia and hypoproteinemic edema frequently were complicating factors. Wound healing was often slow and unsatisfactory, and wound infections were common. Decubitus ulcers were difficult to avoid. A localized pelvic abscess required drainage in one instance. Femoral thrombophlebitis occurred several times. Partial intestinal obstruction complicated convalescence in 3 instances, being relieved in 2 cases by medical measures, including small intestinal intubation, and in the third by rupture of the bowel with spontaneous formation of a fecal fistula which subsequently closed. Adynamic ileus was a terminal development in 2 of the fatal cases. We have observed, as have others,^{5,6} the excessive loss of fluid and chlorides through the ileostomy discharges in the first days following operation. Unless this danger is recognized, marked hypochloremia and dehydration may quickly develop, but they are easily avoided by saline infusions and blood transfusions in the early days of convalescence. Prolapse of the ileum was a frequent late complication of operation. It occurred in 5 out of 20 cases and required surgical repair in 3 instances.

Analysis of Fatalities. Examination of the factors responsible for the fatal outcome in 4 of the 7 patients treated surgically reveals certain features which deserve consideration.

Clinical Abstracts. CASE 1.—I. P. made a highly satisfactory recovery following ileostomy, gaining 76 pounds. Gradual spontaneous closure of the ileostomy 2 years later necessitated re-operation, which was again followed by a gain of 40 pounds and marked clinical improvement. In the following year arthritis developed. A year later fever and jaundice occurred, an hepatic abscess was drained. Death occurred in 3 months and autopsy revealed multiple liver abscesses, peritonitis and bronchopneumonia. The spontaneous closure of the ileostomy could have been avoided by performing complete transection of the ileum with implantation of the proximal portion in the abdominal wall. We regard this as the operation of choice. The development of arthritis and liver abscess probably resulted from the serious infection of the colon. The fatal outcome could, in all likelihood, have been avoided by timely colectomy after the preliminary ileostomy.

CASE 2.—M.H. died with intestinal obstruction and toxic jaundice 5 days after ileostomy and almost complete colectomy in one stage. The fatal outcome is attributed to the fact that the primary operation was too extensive. It emphasizes the belief that the ideal procedure is preliminary ileostomy, with delay of subsequent colectomy until the patient's condition is sufficiently improved to withstand it.

CASE 3.—J.B. was suffering from a fulminating type of the disease. Operation was postponed until it was apparent that death would ensue

without it. The fatality occurred soon after the second stage of the ileostomy from paralytic ileus, dehydration and general sepsis. While the operative mortality is, at best, very high in this type of ulcerative colitis, it is further increased by an unnecessary delay in surgical treatment, and can be reduced only by the closest possible coöperation between medical and surgical attendants.

CASE 4.—I.R. died 1 month after ileostomy in a severe state of malnutrition and hypochloremia. Death was attributed to inadequate post-operative care in a patient who was refractory and uncoöperative. The outcome emphasizes the necessity of constant and patient attention to details of maintenance of proper nutrition, fluid balance and routine nursing care under even the most trying conditions.

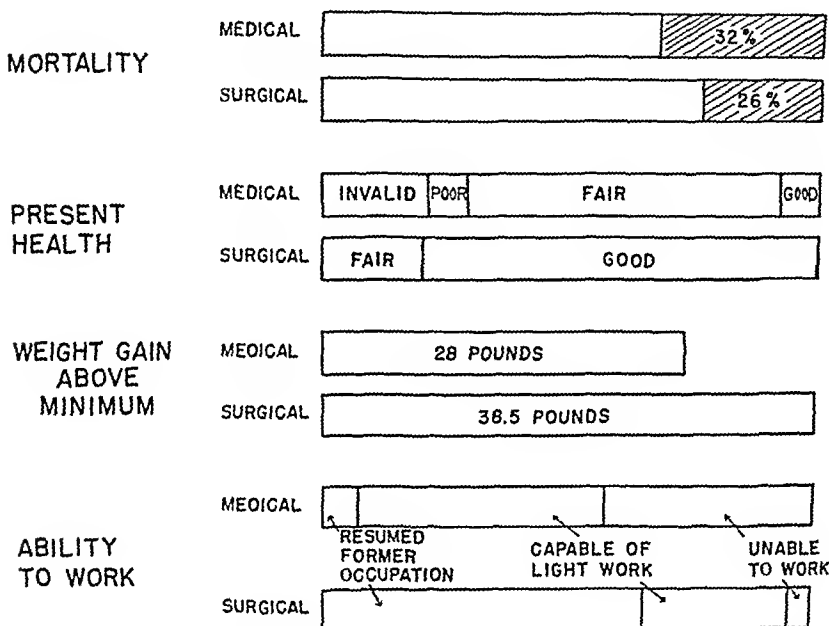


FIG. 2.—Comparative data on the present status of the medically versus the surgically treated patients.

Discussion. These results (Fig. 2), in our opinion, clearly indicate the superiority of surgical treatment in cases of severe ulcerative colitis. We recognize, however, that others do not share our enthusiasm: some,¹ because of greater success with medical therapy, and some,⁹ because of a less favorable experience with surgical treatment. Such a difference of opinion naturally inclines us to subject our own data to doubly critical examination in an effort to discover either erroneous interpretations of the data or factors which might have favorably influenced the results of treatment in one group. We have found nothing to suggest that the surgical cases received preferential treatment in their routine care. Our cases were selected from 3 different services of the hospital, and were under the supervision of a large number of physicians holding varied opinions concerning the ideal method of treatment so that no preference of our

own for or against surgical therapy could, we believe, have influenced the results. The study has extended over a period of 12 years, sufficiently long to give accurate indication of the results of both non-surgical and surgical methods. If errors in interpretation of the data exist we believe that they have resulted in understatement of the success of surgical treatment rather than the reverse. This is true for two reasons, first, because all patients operated on were included in the study whether, in our opinion, adequately or inadequately treated, and also because of the fact that these cases by and large were far more seriously ill than even the most severe cases in the medical group.

A comparison of the surgical results in the first versus the second 6-year period of the study cannot easily be reduced to figures. However, the inadequate operations which gave unsatisfactory results were all done during the earlier period. It is our definite impression that a steady improvement in surgical treatment has occurred, which encourages us to believe that with continued experience present difficulties will ultimately be overcome.

The indications for operation may be regarded as either obligatory or optional. In the former category we include perforation of the colon, those with a fulminating type of the disease, and those who develop complications such as generalized arthritis, repeated hemorrhages from the colon and severe perirectal infection. Little difference of opinion exists here. In the other group, however, in which operation is elective, wide divergence of opinion is expressed. We regard any patient with intractable symptoms, whether intermittent or continuous, who has failed to respond to a reasonable period of medical treatment, as a candidate for surgery. What constitutes a reasonable trial of non-surgical therapy is difficult to state categorically, but our experience suggests that at present surgery is more often unjustifiably delayed than prematurely done.

The mortality rate in the two groups was essentially the same, 32% for those treated medically, 26% for those treated surgically. Since the medical group was selected to include only the more severe cases comparison to the mortality rates in the literature is difficult. The figures included in Willard's review⁸ give mortality rates of from 3 to 35%. Similar figures for cases treated surgically vary from 21 to 73%.

We are in agreement with Cave,⁴ McKittrick and Miller⁷ and others that the most satisfactory results in the treatment of this disease are obtained by a medico-surgical team who are particularly interested in the problems concerned. The reduction in mortality which such a group can bring about has been amply demonstrated. This closer coördination of effort is especially essential in determining the nature of and optimum time for the original operation, in assuring sustained attention to the problems of nutrition while the patient is under surgical treatment, and in deciding upon the necessity for and the extent of the operations which follow preliminary ileostomy.

This disease is one, par excellence, the treatment of which cannot be regarded as primarily medical or surgical without serious detriment to the patient.

Conclusions. Two comparable groups of patients with idiopathic ulcerative colitis have been studied; one received medical treatment only, in the other various side-tracking operations were performed. The mortality in the two groups was practically equal. Comparison of the subsequent developments leads us to the conclusion that those who were operated upon were more nearly restored to normal health than those who were not. The group treated medically has had continued or intermittent manifestations of the disease and is in poor or only fair health. Those operated upon made, in most instances, dramatic recoveries. The great majority returned to their previous occupations, and lead, by their own definition, a normal life. They have expressed satisfaction with their treatment even though it has entailed a permanent external intestinal fistula.

The surgical procedure of choice is a preliminary ileostomy with subsequent colectomy in stages, if indications for it exist. We have discussed some of the causes of unsatisfactory results, the post-operative complications and have emphasized the necessity of close coöperation of internist and surgeon, if the best results are to be obtained.

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COMPLETE ROENTGEN RAY STUDIES OF THE GASTRO- INTESTINAL TRACT IN 400 ARTHRITICS.

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In a recent communication^{4b} attention was directed to a variety of considerations bearing upon treatment of the arthritic and to the further fact that decreasing emphasis upon focal infection as

the chief cause of arthritis has opened the way to fuller appreciation of other influences operative both to produce the disease and to modify the course of it. The present article extends some aspects there touched upon and also continues earlier studies.

One of the present writers^{4a} has previously stressed the importance of considering adequately all deviations of physiology presented by the arthritic. Among these deviations are those to be seen in the gastro-intestinal tract and some phases of this were discussed earlier, together with certain nutritional aspects, by Pemberton and Peiree.⁵

Opportunity now presents, however, for a fuller review of the field on the basis of complete roentgenographic studies of the gastro-intestinal tract in a series of 400 arthritics and 100 normals. So far as the authors are aware no survey of comparable magnitude has been previously conducted and it is reasonable to suppose that the results should indicate whether, and to what extent, the gastro-intestinal tract is implicated, from the Roentgen ray standpoint, in the syndrome of arthritis.

The series of cases studied* represents all types and stages of arthritis and had its beginning about 1920. Analysis of the gastro-intestinal tract was undertaken at that time because of the conviction of one of the authors (R.P.) that focal infection alone did not account adequately for the syndrome and that many other factors played contributory rôles. Among the last mentioned were certain clinical observations that nutritional factors, the balance of food-stuffs and the function of the gastro-intestinal tract as a whole sometimes exercise a determining influence.

Correlation of the roentgenographic data with the clinical state of the subjects is confined essentially in the present report to the two great types into which the field is generally divided; namely, atrophic (rheumatoid) arthritis and hypertrophic (osteo-)arthritis. Fuller correlation with respect to other more detailed clinical data will be made the subject of a later communication.

The usual procedure and technique for gastro-intestinal study were carried out in each case, special attention being paid to the size, position, tone and function of the various organs, as explained later in the text. In many cases findings were checked at subsequent studies and serial studies were carried out at various intervals when indicated, since the positions of organs and, to some degree, the sizes of them are variable, within normal limits, because of differences in body build.

* The earlier roentgenographic studies were conducted mostly in collaboration with Dr. William S. Newcomet, assisted at times by Dr. E. W. Spaekman. Some cases were studied in collaboration with Drs. George E. Pfahler and Bernard P. Widmann. A considerable number of later studies was carried out in collaboration with Dr. J. Donald Zulick, and also with one of the present authors (E. W. S.). Obligation is herewith expressed to the above and to Dr. Newcomet and Dr. Zulick in particular for their valuable and interested coöperation.

At the outset of the present study 100 unselected complete radiographic examinations of the gastro-intestinal tract of arthritics were chosen and the findings analyzed. On the basis of this preliminary survey a detailed plan for further studies was established as shown in Table 2. This plan was then used for the quantitative analysis of the remaining 300 cases in the arthritic series. These findings were then tabulated and compared with a series of 100 normal cases selected from our services at the Presbyterian Hospital, Philadelphia. This series was reviewed to establish the criteria of normal limits, especially in regard to size and position of the various parts of the gastro-intestinal tract. In determining normal standards for this particular problem it is important to consider the build of the patient (Table 1).

TABLE 1.—ROENTGENOGRAPHIC GASTRO-INTESTINAL DATA FROM 100 NORMALS.

	<i>Normal</i>	<i>Asthenic</i>	<i>Sthenic</i>
A—position of lower pole of stomach	Fifth—L	4 cm. below iliac crest	Third—L
B—position of cecum	Middle third of iliac fossa	Lower third of iliac fossa	Upper third of iliac fossa
C—position of hepatic flexure . .	Third—L	Only slightly above crest of ilium	Second—L
D—position of splenic flexure . .	First—L	Second—L	Twelfth—D
E—position of sigmoid	Below first sacral segment	First sacral segment	Below first sacral segment

Upper and Lower Limits of Normal Width of Colon.

Cecum	4 to 6 cm.	Descending . . .	3½ to 5 cm.
Ascending . . .	4 to 6 cm.	Pelvic	3 to 5 cm.
Transverse . . .	3½ to 6 cm.	Rectum	6 to 8 cm.

It is well recognized that the asthenic type of individual often presents features suggestive of enteroptosis, whereas the more sthenic type does so less often. Some consideration must therefore be exercised towards what is to be considered as normal for the asthenic type and, by the same token, for the sthenic type. On the other hand, given this distinction, standards of normality may still be loosely applied in evaluating Roentgen ray studies of the gastro-intestinal tract. Thus, it by no means follows that a condition of marked enteroptosis, together with redundancy and sharp angulation of the colon, encountered in a person of asthenic type, is to be regarded as wholly normal and provision was therefore made to evaluate such departures.

The normal series consisted very largely of symptom-free patients

who were referred for gastro-intestinal study as part of a general checkup examination and generally complained of nothing directly referable to the digestive system. Thirty-two of these patients were normal as to general body build, 20 were sthenic in type, and 48 were asthenic. Table 1 indicates the upper and lower limits as to size and position of the organs for all three types. The width of the various portions of the colon showed less variation due to the body build than did the position of the flexures, and the limits determined in the diameter of the colon were therefore merely upper and lower limits of normal for these measurements irrespective of the patient's build. From the analysis of the 100 normal cases the values occurring with the greatest frequency were computed and these data comprise the basis for Table 1.

TABLE 2.—RESULTS OF PRELIMINARY STUDIES ON THE GASTRO-INTESTINAL TRACT OF 100 ARTHRITICS, INDICATING POINTS TO BE NOTED IN ROUTINE STUDIES.

Esophagus:

No findings of interest in arthritics.

Stomach:

Structure—size, position, type.

Function—peristaltic activity, character of waves.

Special—tenderness, irregularities and defects, retention at 6-hour period.

Duodenum:

Structure—size, position.

Function—emptying time, tone, peristaltic activity.

Special—defects, tenderness, dilatation, irregularity or delay and other duodenal loops.

Gall bladder:

Structure—size, position and regularity of outline.

Function—absorption, concentration and fat response.

Special—tenderness, calculi, fixation, flexibility.

Small Intestines:

Structure—general pattern.

Function—distribution at the 6-hour interval, residue at the 24-hour interval, and motility.

Special—tenderness, irregularity in pattern, defects.

Colon:

Structure—size, position, haustral appearance; individual parts studied were the cecum, ascending, transverse, descending and pelvic colon, rectum and flexures.

Function—tone and motility.

Special—defects, comparative study of position of various parts in lying and standing postures, position of appendix and ileocecal valve, regurgitation.

Having estimated the criteria for normals, 300 cases of arthritis of both types were studied from the services of the writers at the Presbyterian Hospital, Philadelphia, the Abington Memorial Hospital, Abington, Pa., and from their private practices. Note was made of all variations from normal, comparing the arthritics with the normal standards, above described, but without reference to the type of arthritis, stage of the disease or any other clinical features of the case. The various features of this analysis are outlined in Table 3.

The findings in the 300 cases analyzed in this manner were tabulated and the results compared with the original 100 cases

examined at the beginning of the study. Inasmuch as close correspondence of the figures for the two groups was obtained the findings were therefore considered to be reasonably representative of arthritics as a group. Review of the data thus obtained reveals that chronic arthritis, irrespective of type, is associated with a certain set of features or deviations from the norm, revealed by Roentgen ray examination of the gastro-intestinal tract, which might almost be called an "arthritic pattern." No single feature noted is typical of rheumatoid disease but a combination of features is so constant that it can be regarded as a significant part of the general picture of chronic arthritis.

TABLE 3—SUMMARY OF THE PRINCIPAL ABNORMALITIES ENCOUNTERED IN THE GASTRO-INTESTINAL TRACTS OF 300 ARTHRITICS *

<i>Esophagus:</i>	No of Cases
No findings of importance	
<i>Stomach</i>	
Abnormalities of structure and position . . .	92
Abnormalities of function	99
Abnormalities in special group (especially defects)	16
<i>Duodenum</i>	
Abnormalities of structure	27
Abnormalities of function (especially irritability and spasm)	184
Abnormalities of special group (especially ileus)	4
<i>Gall bladder:</i>	
Abnormalities of structure and position	237
Abnormalities of function	281
Abnormalities in special group (especially calculi)	44
<i>Small intestines</i>	
Abnormalities of structure	2
Abnormalities of function (especially in distribution of barium at the 6- and 24-hour periods)	204
<i>Colon:</i>	
Abnormalities of structure and position	361
Abnormalities of function (especially excessive regurgitation and abnormal retention after passing)	201
Special group (especially defects)	28

* Attention is directed to the fact that one organ such as the stomach or gall bladder may present several deviations from normal. For purposes of brevity the sum of deviations is presented, even though such a sum may suggest undue extent or frequency unless this fact is kept in mind. A detailed consideration of these deviations will be made the subject of a later communication.

The extent of deviations from normal within the gastro-intestinal tract is not necessarily, but usually, in accord with the general condition of the patient. The deviations are generally more pronounced in advanced cases and less marked in early cases. There is no distinctive aspect of any of the several features studied characteristic "*per se*" of arthritis, *e. g.*, pyloric irritability and duodenal spasticity, when present, appear in arthritis precisely as they do, when present, in gastric or duodenal ulcer, disease of the gall bladder, appendicitis and other local or systemic conditions.

Abnormalities appear in either the gall bladder, stomach or small intestine in about 60% of cases. The complex most nearly characteristic of the arthritic syndrome is seen in relation to the colon.

At least 80% of arthritic cases present deviations from normal in this region. Two general phases of gastro-intestinal tone or balance, with intermediary gradations, are to be observed; namely, atonicity and spasticity. Hypotonic manifestations of part or all of the colon occur in about 40% of the series and completely atonic manifestations in nearly 10%. Occasionally one part of the colon shows atonicity while another shows spasticity.

TABLE 4.—SUMMARY OF DATA REGARDING ABNORMALITIES IN VARIOUS ORGANS FROM THE ROENTGEN RAY STANDPOINT.

Esophagus:

No important deviations from normal appear except spasm.

Stomach:

Ptosis, dilatation, flabbiness, hypotonicity, changes in motor mechanism are frequently present (20% to 30%). Other features such as irritability, spasm, are often present but are regarded as of minor significance.

Duodenum:

Hypotonicity and irritability are commonly found (15%); fixation, tenderness, delay and organic deformities are less frequent (3% to 5%).

Gall bladder:

Ptosis, dilatation, subnormal absorption, subnormal concentration and response to fats or even non-function may appear. One or more of these departures from normal was observed in over 50% of the subjects studied. Other data have been encountered which may be considered as indicative of possible infection, past or present, such as adhesions. Calculi are sometimes found (approximately 10%).

Small intestine:

Disturbance of motor function in respect to either hyper- or hypoactivity is more commonly found than is any other feature in this region (15% to 20%):

Colon:

Cecum: Dilatation, atonicity and ptosis are the most frequent and characteristic features (80%).

Ascending colon: Dilatation, haustral irregularity, hypotonicity are common; sometimes irritability is present.

Hepatic flexure: Ptosis, hypermobility, folding and redundancy are frequently present.

Transverse colon: Ptosis, hypermobility, folding, haustral irregularity and spasms are common.

Splenic flexure: Elongation and redundancy are commonly noted.

Descending colon: Narrowing of lumen, haustral absence or irregularity, spasm, folding, sometimes associated with local tenderness or rigidity, are observed.

Sigmoid: High looping and excessively redundant type with dilatation is characteristic.

Rectum: Dilatation is common.

In order to determine whether any feature of the gastro-intestinal findings differentiates the two types of arthritis or accompanies chiefly one or the other type, 100 unselected cases were reviewed, 58 being of the atrophic variety and 42 of the hypertrophic variety. No such correlation was evident. Apparently the deviations from normal in the gastro-intestinal tract are similar in all essential respects in each variety.

Table 4 gives a summary of the main findings in the series of 400 cases under investigation.

Certain of the patients who exhibited slight clinical manifestations of arthritic activity at the time of examination presented from the gastro-intestinal standpoint a pattern comparable to that char-

acterizing severe arthritis. Some of these patients subsequently developed notable clinical activity in respect to arthritic manifestations. Whether such conditions in the gastro-intestinal tract can be regarded in any sense as predisposing factors cannot be definitely ascertained from the present study alone.

It can be fairly said, however, that in the study of arthritic cases at large, recognition of the type of variation in the radiologic field here discussed may definitely assist the clinician in estimating the extent to which a background of constitutional or structural weakness may be present in given cases. The results of the present study are not to be regarded as of diagnostic value but when obvious precipitating factors are absent, such as marked focal infection and the like, it becomes proper to give greater emphasis to the gastro-intestinal findings and to the varied implications which they bear in a systemic as well as a local sense.

Parallel with the general course of the uninfluenced disease there is a tendency for some of the deviations of the gastro-intestinal tract above described to become more marked, particularly as regards ileal stasis and the configuration of the large bowel. This tendency is recognizable as concomitant with chronic disease of several kinds and, as remarked earlier, the deviations described in the foregoing text can be in no sense regarded as confined to or pathognomonic of the arthritic syndrome. It is perhaps superfluous to add that appreciation of this last mentioned fact in no wise obviates the necessity of evaluating the above deviations and determining their significance from the etiologic, pathologic and therapeutic standpoints. It may be well, however, to point out that the influence of abscessed teeth, or an infected prostate, in precipitating arthritis is well recognized although such foci of infection are also to be found in countless persons in apparent health. Indeed, one of the difficulties characterizing some approaches to understanding and treatment of the arthritic syndrome has been an "all or none" attitude on the part of some observers. The fact that deviations of nutrition and of the gastro-intestinal tract do not explain all the phenomena of arthritis has led to a form of negation which has minimized such considerations in spite of the further fact that parallel developments in the field of nutrition at large and in the gastro-intestinal tract and the deficiency diseases in particular, testify to an intimate and delicate balance between the processes there operative. Deviations from the processes of normal nutrition, at any link of the chain, may not only be significant on their own account, alone and in combination; they may even determine the existence of an infectious process and conditions its influence. Viewed in this light apparently minor departures from normal of anatomic or physiologic nature must be accorded a potential significance far beyond the surface implications.

Thus, by way of illustration, the roentgenographic findings as

regards the colon afford explanation, and some corroboration, of studies conducted by Stabler and Pemberton⁶ which revealed that the bacterial count of the feces among arthritics was definitely higher than among normals, although the kinds and proportions of organisms showed no great differences. The full significance of this correlation is not yet apparent but it is to be noted that McCarrison³ and others have induced in the large bowel of monkeys, by diets inadequate in vitamin B, a similar picture of elongation, dilatation and redundancy. This anatomic deviation can be carried on experimentally to changes in the mucosa amounting to colitis and in such animals there is clear evidence of the passage of bacteria through the walls of the gut with involvement of lymphatic nodes. It is not to be supposed that this situation has been demonstrated in its entirety in arthritics, though in advanced cases much of the picture may be observable clinically, and volvulus or intussusception, with obstruction, has been met in several of the cases forming the basis of the present report.

Elongation and dilatation of the large bowel are referable to atonicity of the 3 so-called "muscular bands" of the colon and this is a function not only of certain avitaminoses, particularly B Complex, but also of the balance of the autonomic nervous system.

It is common knowledge to close students of arthritis that the nervous system may play an important rôle in precipitating or perpetuating the disease and that part of the accepted value of conditioned rest in the treatment of arthritics finds explanation in the influence it exerts on the nervous system. This influence is achieved partly through the removal of undue stimuli, but is reciprocal with other factors such as the dynamics of the circulation, the extent to which optimal nutrition is approached, the presence of infection, and so on. In this general connection reference should here be made to the fact, first brought out by Fletcher¹ and corroborated by Pemberton and Peirce⁵ that, as arthritics showing dilatations and redundancies of the bowel undergo convalescence, striking changes in configuration and function of the bowel may occur, so that serial roentgenograms present marked contrasts, the later ones being hardly recognizable in terms of those first taken. Further evidence indicating the significance of these general findings is probably to be found in the occasional value of colonic irrigation in the treatment of selected cases of arthritis. In any event, the data at hand do not permit strong negative postulates that deviations in configuration, position and function of the colon of the extent mentioned can have no bearing upon physiologic processes with which that organ is primarily and secondarily concerned. On the contrary, the data herewith submitted indicate strongly, what clinical experience has long borne out, that arthritics as a group are accompanied by dysfunction of the gastro-intestinal tract, chiefly in the lower bowel, but also elsewhere, which is not

only susceptible of betterment but should be included in any wide-angled therapeutic approach to the problem as a whole. There is no opportunity here to discuss the measures available to this end. Suffice it that they centre around conditioned rest, equilibrium of the nervous system, optimal nutrition, including adjustment of the balance of the foodstuffs, the establishment of normal gastro-intestinal function and control of the influence of infection, if any.

These considerations are not to be interpreted as implying that the gastro-intestinal deviations described, when present, constitute the chief factors to which attention should, in the care of arthritics, be given. On the contrary, they may in many instances be of academic interest only. On the other hand, in some instances in the series under discussion, therapy directed at more obvious factors proved unavailing and convalescence was initiated only when the gastro-intestinal tract was made the object, directly and indirectly, of intensive care. Such well marked deviations of the gastro-intestinal tract as a sluggish, not to say obviously infected, gall bladder usually receive appropriate study and treatment. This is not so usual, however, in cases of arthritis showing minor degrees of gastric retention, intestinal stasis or colonic stasis or enteroptosis. The incidence of achlorhydria has been shown by Hartung and Stein⁴ to be 17% in atrophic and 28% in hypertrophic arthritis. Achlorhydria has been found by the same investigators in 3% of atrophic and 36% of hypertrophic arthritics. Replacement therapy here may have valuable consequences. The simply achieved but graphic influence of rest in recumbency upon a ptosed stomach or redundant and folded colon may be very significant.

It is the conviction of the writers that rectification of these and other departures from normal in the gastro-intestinal tract cannot be expected to have graphic results, or indeed any consequences, unless conducted in conformity with a balanced plan of therapy which considers all aspects of the problem, beginning usually with bed rest, and coördinating from then on all measures brought to bear.

Space does not permit of enlarging here further upon the importance of this attitude towards the therapy of arthritis which has been set forth in previous communications.^{4a, b, 5} Whether or not the several deviations of the gastro-intestinal tract above discussed underlie the syndrome at times or are invariably consequences of it, the fullest possible rectification of them is a biological indication all too frequently ignored or overlooked. Only benefit in a wide sense can accrue from such practice and the clinical evidence is unmistakable that in certain cases of arthritis the influence of such considerations is not only contributory but even a *sine qua non* of successful therapy.

Summary. 1. Roentgenographic study of the gastro-intestinal tract has been conducted upon 400 arthritics and upon 100 control subjects. Upon the basis of data afforded by the control subjects,

reference points have been established for the various positions of parts of the tract and for limits of function.

2. Among arthritic subjects, deviations from normal structure and function have been encountered in the stomach, gall bladder, small intestine, or in some combination of these, in approximately 60% of the cases. The complex most nearly characteristic for arthritis is seen in the colon which presents ptosis, dilatation and/or atony in 80% of cases.

3. No one of the above deviations is typical of rheumatoid disorders but a combination of them constitutes a more or less definite pattern in severely ill arthritics. There is a tendency for these deviations to parallel the general condition of the patient.

4. Whether the deviations discussed underlie the syndrome or are consequences of it, rectification of them is a clinical indication.

5. The measures necessary to this end are varied and must be coördinated. Apart from care of the gastro-intestinal tract *per se* in respect to hydrochloric acid replacement, lubrication, provision of bulky food, and so on, therapeutic measures must centre around systemic rest, equilibrium of the nervous system, optimal nutrition, the control of infections, and a balanced plan of therapy which considers all aspects of the problem and of the patient.

6. Neglect of the philosophical and therapeutic considerations inherent in these findings accounts for much of the difficulty experienced in treatment of arthritics as a group.

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THE RELATION BETWEEN PLASMA AND DIETARY ASCORBIC ACID.

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NUMEROUS experimental studies have demonstrated that in the guinea pig the ascorbic acid content of the tissues is dependent upon the amount of the vitamin administered as a supplement to the

scorbutogenic diet.^{6,11,13,15,23} Similarly, in the case of human subjects, most investigators have found that the concentration of the plasma ascorbic acid reflects the level of the dietary intake,^{1,3,12,14,16,21} although the quantitative aspects of this relation have not been clearly defined. In the present investigation we have sought to characterize more exactly the relation between plasma and dietary ascorbic acid levels in healthy human subjects aged 12 to 35 years who were following their usual dietary habits.

Methods. The plasma ascorbic acid concentration was determined by indophenol titration of metaphosphoric acid filtrates under conditions essentially similar to those of the macro method of Farmer and Abt.¹⁰ Oxalated blood samples were collected from subjects in the fasting state; potassium cyanide was not used, as it has been reported to be unnecessary and to lead to error.

The estimation of the average daily intake of ascorbic acid in the diet was a more difficult matter. Our subjects followed their usual dietary habits, and, for a period of 10 to 14 days, kept a careful record of the weights of all foods consumed, using a spring balance for that purpose. We found it necessary to prepare our own conversion table for use in translating these records into terms of the average daily ascorbic acid intake. As reported elsewhere,⁴ our conversion table is based on figures obtained from the literature, but is heavily weighted to favor our own analytical values for the ascorbic acid content of foods similar in respect to variety, brand, season, storage, preparation and cooking to those eaten by our subjects. Over 500 samples of prepared food were analyzed for this purpose, and the technique and possible accuracy of our estimates are discussed in the reference cited.

Only subjects free from acute or chronic medical disease were selected for this study. Their state of health was assessed by an interview in which their previous medical history was reviewed and such physical examination performed as was indicated.

In all, we are reporting 65 correlations of the plasma and dietary ascorbic acid levels of 56 individual subjects. Of these, 33 were student dietitians, medical students, or laboratory workers, while 23 were hospital out-patients free from medical disease, and obtained for the most part from the Walter G. Zoller Memorial Dental Clinic through the courtesy of Dr. James R. Blayney. The total material is divided into two groups as follows:

Group I consists of 41 correlations of the plasma and dietary ascorbic acid levels of 36 individual subjects. Of these, 22 were males and 14 females; 15 were between the ages of 12 and 19 years, while 20 were from 20 to 35 and one subject was 42 years old. In this group a plasma determination was made at the beginning and end of a 10 to 14-day weighed diet record, and only those cases included in which the two plasma determinations agreed within 0.2 mg. per 100 cc. Group I comprises our more accurate correlations.

Group II includes 24 correlations in 20 additional subjects, and is set aside from Group I either because the diet record was kept in terms of measured rather than weighed portions (a less accurate method), or because only a single plasma determination was done, and it is less certain that the subject was in equilibrium with his diet.

All subjects are included in this report except those excluded (a) because they fell outside the specified age group, 12 to 35 (42) years; (b) for reasons of health; or (c) because their two plasma determinations differed by more than 0.3 mg. per 100 cc. and equilibrium with the diet was questioned.

Results. The results of this study are presented as scatter-point diagrams (Charts 1 and 2), in which the average daily intake of

ascorbic acid per kilo of body weight is plotted against the average plasma ascorbic acid for the period studied. Chart 1 presents the 41 correlations of Group I, while Chart 2 presents all 65 correlations of both groups. Taking into account errors inherent in our method, we consider that Charts 1 and 2 satisfactorily demonstrate the close dependence of the plasma concentration on the vitamin intake per

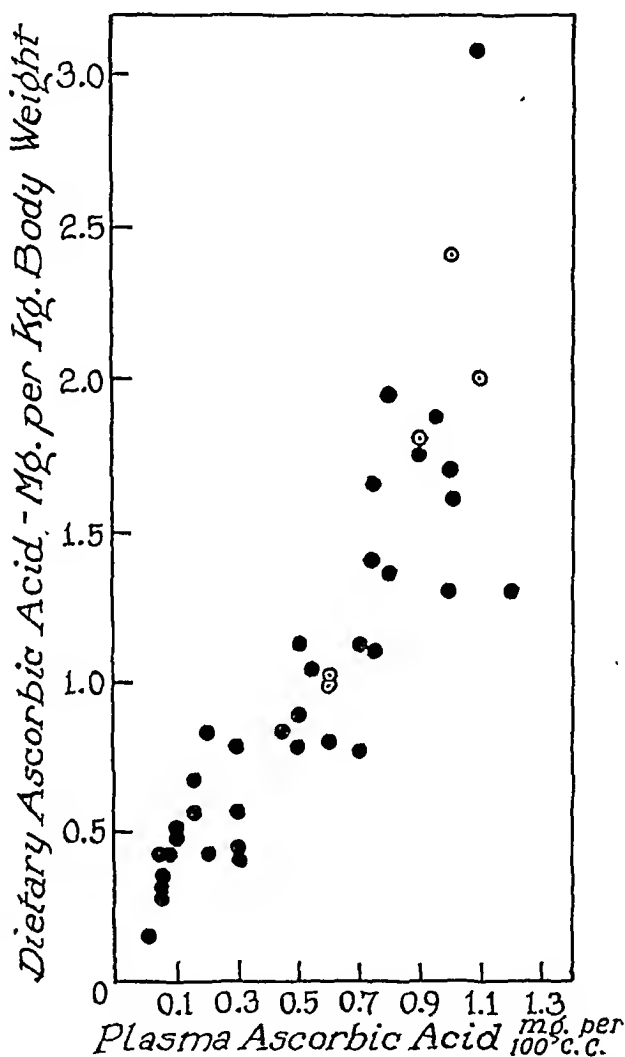


CHART 1.—Correlation of the fasting plasma ascorbic acid concentration with the average daily intake of ascorbic acid per kilo of body weight (Group I).

kilo of body weight. At least three types of error may affect the observed relation between the dietary and plasma level and hence cause undue dispersion of the points on the graph. First, it is our experience that repeated plasma determinations in a subject receiving a known, constant daily intake of the vitamin may vary by as much as 0.2 mg. per 100 cc., and the technical error of the

method is 0.1 mg. per 100 cc. Second, the value here assigned to the ascorbic acid intake is an estimate rather than a direct determination. Finally, the eating habits of many of our subjects were somewhat irregular in respect to vitamin C, and it may be questioned whether in these cases their plasma had always attained complete equilibrium with their dietary ascorbic acid.

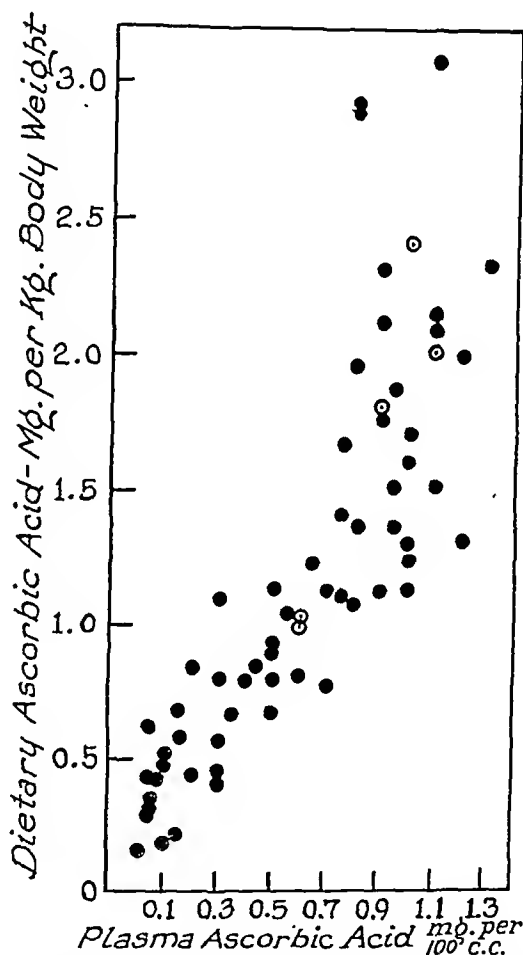


CHART 2.—Correlation of the fasting plasma ascorbic acid concentration with the average daily intake of ascorbic acid per kilo of body weight (Group I plus II).

It will be noted that we have expressed the ascorbic acid intake in terms of milligrams per kilo of body weight. If we plot instead, the total average daily intake regardless of body weight we obtain a wider scatter of experimental points than is noted in Chart 1. We have also tried plotting the relation between plasma concentration and the daily ascorbic acid intake both per square meter of body

surface and per 100 calories of calculated basal metabolism, and we find in each case a correlation which approaches more nearly that seen in the charts here published. We believe, however, that the unavoidable variability of our data makes it impossible to decide from comparisons of this sort whether or not the metabolic rate is as important as body weight in determining the requirement for ascorbic acid. Animal studies are likewise inconclusive on this point. In guinea pigs weighing from 120 to 1040 gm., Dann and Cowgill⁸ found that the amount of vitamin C necessary to protect against scurvy was directly proportional to the body weight, and little, if at all, influenced by the metabolic rate. But others have shown that thyroid feeding increases the dose of vitamin necessary to protect guinea pigs against scurvy,¹⁹ and decreases the amount of ascorbic acid to be found in their tissues.^{9,17,20}

Returning to our charts, it will be noted that the plasma concentration increases in a more or less linear fashion with increasing dietary intake until the latter reaches a value in the neighborhood of 1.7 to 1.9 mg. per kg., and the plasma approximates 1.0 mg. per 100 cc. A further rise in the intake has much less effect on the plasma level. This abrupt change in the correlation between intake and plasma concentration is, of course, a reflection of the condition widely discussed in the literature under the term "saturation," in which the tissue "stores" are considered to be full, and the body responds to a large test dose of ascorbic acid by excreting in the urine a good proportion of the extra vitamin administered.

Other workers have determined by different techniques the amount of vitamin C necessary to maintain saturation in healthy adults and their results tend to confirm our findings. Ralli, Friedman and Sherry,¹⁸ for example, found in extended studies of 3 experimental subjects that the ingestion of 100 mg. of ascorbic acid a day caused a maximum retention of the vitamin and stabilized the plasma concentration at or above 1.0 mg. per 100 cc. Although Ralli and co-workers do not consider body weight a factor, if we take the liberty of calculating intake per kilo from their report we obtain 1.4 to 1.6 mg. per kg., figures approaching those indicated in Chart 1. Also, Belser, Hauck and Storvick² and Todhunter and Robbins²² found in experiments of shorter duration that saturation, as judged by the urinary response to a test dose, could be maintained by intakes of 1.2 to 1.7 mg. per kg. (7 subjects), and 1.6 to 1.7 mg. per kg. (3 subjects), respectively.

Indeed it should be possible to predict from Chart 1 the daily intake necessary to stabilize an individual at a given level of plasma ascorbic acid. To test this point the experiments presented in Table 1 were performed. The plasma concentrations of 5 normal subjects were adjusted to the levels to be tested by increasing or decreasing their vitamin C intake. Each was then given a diet practically devoid of the vitamin together with a supplement of

synthetic ascorbic acid or titrated fruit juice at each meal such that his total daily intake was that indicated in Chart 1 as necessary to maintain the new plasma level. The experiments were continued for 10 or 11 days, except for one which lasted 25 days, and in no case did the plasma value vary by more than 0.2 mg. per 100 cc. The 5 correlations of plasma and dietary ascorbic acid obtained in this way are included in Charts 1 and 2 as hollow circles in place of the solid dots which represent the other correlations.

TABLE 1.—THE DAILY INTAKE OF ASCORBIC ACID NECESSARY TO STABILIZE THE FASTING PLASMA ASCORBIC ACID AT A GIVEN LEVEL.

Subject.	Sex.	Age.	Weight, kg.	Average fasting plasma ascorbic acid, mg. per 100 cc.	Daily intake of ascorbic acid.		Duration of experiment, days.
					Total, mg.	Per kilo body wt. mg./kg.	
1	M	21	66	0.6	66	1.0	25
2	M	24	68	0.6	69	1.0	11
3	M	20	82	0.9	150	1.8	11
4	M	15	40	1.0	95	2.4	10
5	M	22	59	1.1	118	2.0	11

Discussion. The results presented in this paper indicate that in normal human subjects, 12 to 35 years of age, who are in equilibrium with their diet, the level of the plasma ascorbic acid in the fasting state is a function of the average daily intake of ascorbic acid, the latter perhaps best expressed as intake per kilo of body weight. For this reason, the determination of the fasting plasma ascorbic acid in the healthy subject provides a useful tool in nutrition studies as it helps to characterize in an objective way the subject's previous diet. Repeated plasma determinations offer an indication of whether or not an individual has attained equilibrium after a significant change in his vitamin C intake. The effect of various pathologic processes on the relation between plasma concentration and dietary intake of ascorbic acid requires further study.

It should be noted that the fasting plasma ascorbic acid runs its full gamut of change, and reaches zero, a good while before any signs of clinical scurvy can be found. Thus Crandon, Lund and Dill⁷ reported that the first symptoms of scurvy appeared in their experimental subject after his plasma concentration had been zero for 120 days, and after he had been completely deprived of vitamin C for 161 days. Butler and Cushman⁵ have advocated the determination of the apparent ascorbic acid content of whole blood, or of white cells plus platelets, as an index of vitamin C deficiency extending beyond the limits imposed by the disappearance of ascorbic acid from the plasma. Nevertheless, in our experience, plasma concentrations of less than 0.1 mg. per 100 cc. have been associated with very low intakes of ascorbic acid, 5 to 20 mg. a day, so that even under these circumstances the plasma determination helps to characterize the diet.

Summary. 1. In healthy human subjects, 12 to 35 years of age, who are in equilibrium with their diet, the level of the fasting plasma ascorbic acid is a function of the average daily intake of the vitamin, the latter perhaps best expressed as intake per kilo of body weight.

2. Saturation, with a plasma concentration of approximately 1.0 mg. per 100 cc., occurs with intakes in the range of 1.7 to 1.9 mg. of ascorbic acid per kilo. With lower intakes the plasma level varies directly with the intake; higher intakes cause little further increase in the plasma.

3. From the data here reported, the daily intake of ascorbic acid necessary to stabilize a normal individual at a given level of plasma concentration may be predicted.

4. Determination of the fasting plasma ascorbic acid affords a useful, objective method of characterizing the diet of the normal individual in regard to his previous vitamin C intake.

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EFFECTIVENESS OF METHYL TESTOSTERONE ADMINISTERED ORALLY.

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It has been repeatedly demonstrated that testosterone therapy, in the form of testosterone propionate, administered by injection has proved to be of definite value in the treatment of certain hypo-

gonadal states, such as eunuchs, castrates, eunuchoidism, and the like. Also, investigations and studies on inunction and implantation therapy are being made. Needless to say the most desired step now would be the evaluation of oral therapy of some form of testosterone. In 1937, Foss^{2a} attempted oral administration of testosterone in a castrate of 38 years, after successful treatment by injections. Plain testosterone in dosages up to 100 mg. per day, has little or no effect on potency. As a further proof of oral inefficacy of glandular preparations, Dodds¹ concluded that all desiccated protein preparations of organs, except that of thyroid, were inactive.

In 1938, Miescher and Tschopp³ discovered that methyl testosterone was considerably more active by mouth than any of the other preparations previously investigated, namely, testosterone, androstenediol, androstenedione, testosterone propionate, and androsterone. This was demonstrated by the increase in the weight of seminal vesicles and prostates of castrated male rats. They suggested that possibly greater protection of the active hydroxyl group from fermentative influences in the alimentary tract was acquired from the adjacent methyl group.

Foss^{2b} again was among the first to try this preparation clinically. He demonstrated that it was able to maintain excellent potency in a post-pubertal eunuch with 100 mg. methyl testosterone by mouth daily, using 10 mg. tablets. Doses of 50 mg. methyl testosterone, daily, maintained fair to adequate potency. This dose was far superior to 100 mg. of plain testosterone. Excretion tests showed adequate utilization and maintenance of dose levels. Foss^{2b} further tried it on hypogonadal boys, with and without obesity. The dose varied from 25 to 50 mg. per day, and he reported satisfactory results. In women, methyl testosterone was found of distinct value in some cases of dysmenorrhea. No specific toxic effects were noted aside from some slight gastric irritation, nausea, anorexia, but relieved by alkaline medication.

Having obtained a supply of methyl testosterone,* we decided to use it in several different types of cases, as follows: 1, as primary treatment in a mild eunuchoid, aged 18; 2, as a maintenance therapy in a patient with hypopituitarism associated with hypogonadism, who had already made startling progress with testosterone propionate by injection; 3, as primary treatment in a case of hypopituitarism with stunting of growth and hypogonadism; 4, as primary treatment in a 16½-year-old post-operative eunuchoid (following operation for hernia and undescended testes); and, 5, as primary treatment in a 22-year-old eunuchoid.

Case Abstracts.—CASE 1. E. S., aged 18, presented himself on December 15, 1939, because of lack of supra-pubic, axillary and facial hair, small penis, high pitched voice, absence of the normal libido for this age, and no

* The methyl testosterone was supplied by Schering Corporation, through the kindness of Dr. Max Gilbert.

history of erections. He was 70 inches tall. Physical examination was otherwise negative. He was placed on 150 mg. methyl testosterone by mouth per day, taken as 50 mg. three times daily. Within 3 weeks there was definite enlargement of the penis, increase in supra-pubic and axillary hair, and numerous erections. Because of a phimosis, it was decided to perform a circumcision, and so the methyl testosterone was stopped after 1 month to permit a subsidence of erections and libido. With the discontinuance of therapy, there was a distinct decline in the erections, libido, hair, growth, and so on.

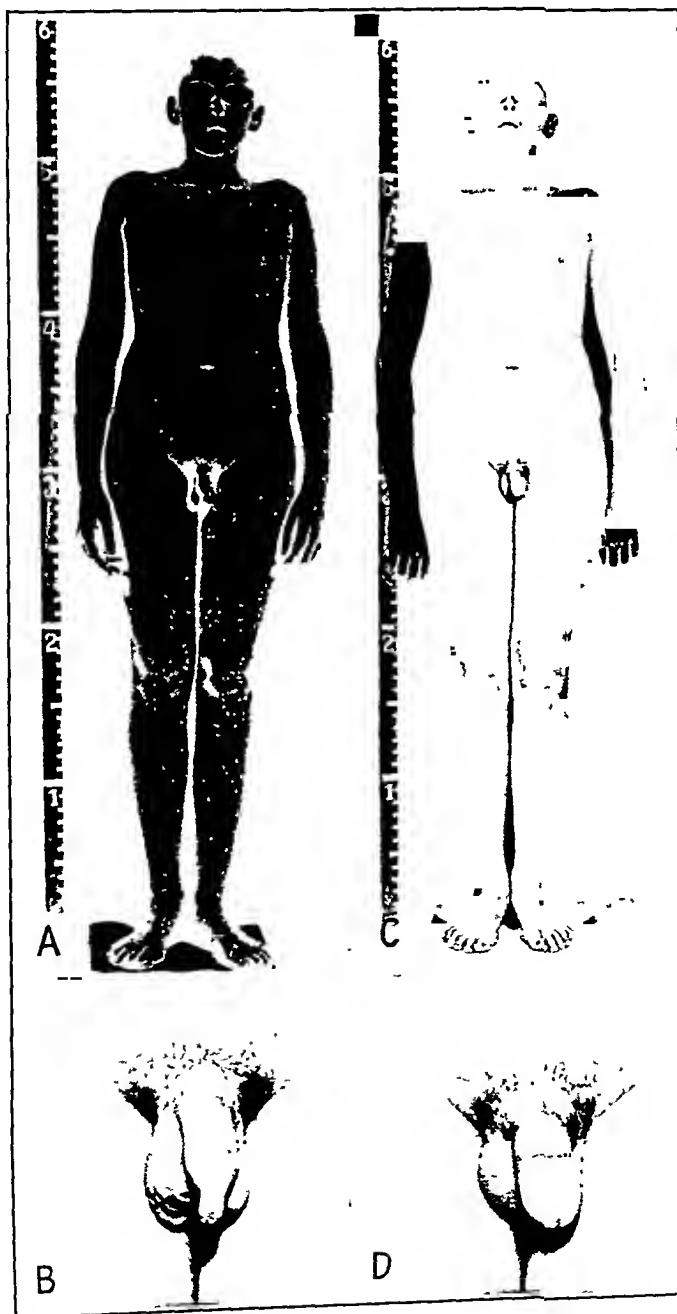
CASE 2.—M. E., aged 14, was an example of Lorain-Levi Infantilism. Because of definite retardation in growth, treatment with growth hormone (Phyone) was commenced at the age of 8, and continued for 1 year. After a year without treatment, injections were resumed, using Antuitrin-G and Antuitrin-S. From the age of 10 to 14, treatment had been continued off and on, and his height increased from 40 inches to 48 inches, but at 14, his genitalia remained those of a child of 6. He was in the fifth term high school, bright and intelligent, had a very high pitched voice and no facial, axillary or supra-pubic hair. He had never had an erection. The testes were barely palpable, the scrotum exceedingly small. He appeared to be about 6 or 8 years of age. The physical examination was otherwise negative. Roentgen ray photographs of the wrists revealed bones somewhat small for the age, and epiphyseal development relatively normal. The sella turcica was within normal limitations, shape and size. From October 1, 1939, to December 9, 1939, he received injections of Growth Complex (Ayerst, McKenna and Harrison) 5 cc. twice weekly, and 22 injections of testosterone propionate (Oreton), 25 mg. each. The changes were so striking that they challenge description (see photographs). At this point, December 15, 1939, he was placed on 150 mg. methyl testosterone per day (50 mg. three times daily), and this was continued to May 7, 1940. The effects of testosterone as demonstrated originally by the injections were continued—growth of genitalia, growth of hair, increasing depth of pitch of voice, growth of 4 inches in height, gain of 17 pounds in weight, complete change in configuration, appearance, and so on. From May 7, 1940, to October 15, 1940, he was without treatment. There was slight regression during this period—number of erections were reduced, and the amount of supra-pubic hair was slightly decreased.

CASE 3.—C. B. came under observation on September 22, 1939, aged 18. His family history and his previous history is of no consequence. He had always been shorter than other boys of his age, and his sexual development was that of a boy of about 8 years of age. Weight was 105 pounds. Height was 57 inches, span 60 inches, and the measurement from superior symphysis pubis to floor 29 inches, and from superior symphysis pubis to vertex 28 inches. There was no facial, axillary or supra-pubic hair. His voice was high pitched, his breasts were slightly enlarged. His penis was very small, the left testicle was in the scrotum but pea sized, and the right testicle could not be felt. Physical examination was otherwise negative (see photographs). Blood pressure was 110/76. His basal metabolic rate was -7% . The blood count was normal. Sugar tolerance curve: 1 hour, 70; 2 hours, 95; 3 hours, 90. Roentgen ray study revealed a delay in epiphyseal ossification. From October 31, 1939, to March 1, 1940, he received 1 cc. Anteron (400 U.) and 2 cc. Pituitary Alkaline Extract (Squibb), each three times weekly, without any change whatsoever. He was then placed on methyl testosterone 150 mg. per day, by mouth, for 5 months. The changes were striking—change in contour, configuration, genital growth, both testes are now palpable and larger, voice pitch lower, growth of supra-pubic and axillary hair, growth of 2 inches in height,

CASE 4.—S. B., aged $16\frac{1}{2}$, came to the clinic February 16, 1940. His family history was irrelevant. At 9 years of age an operation was performed for bilateral herniæ and undescended testes. There is no note as to

E. S.—12/21/39

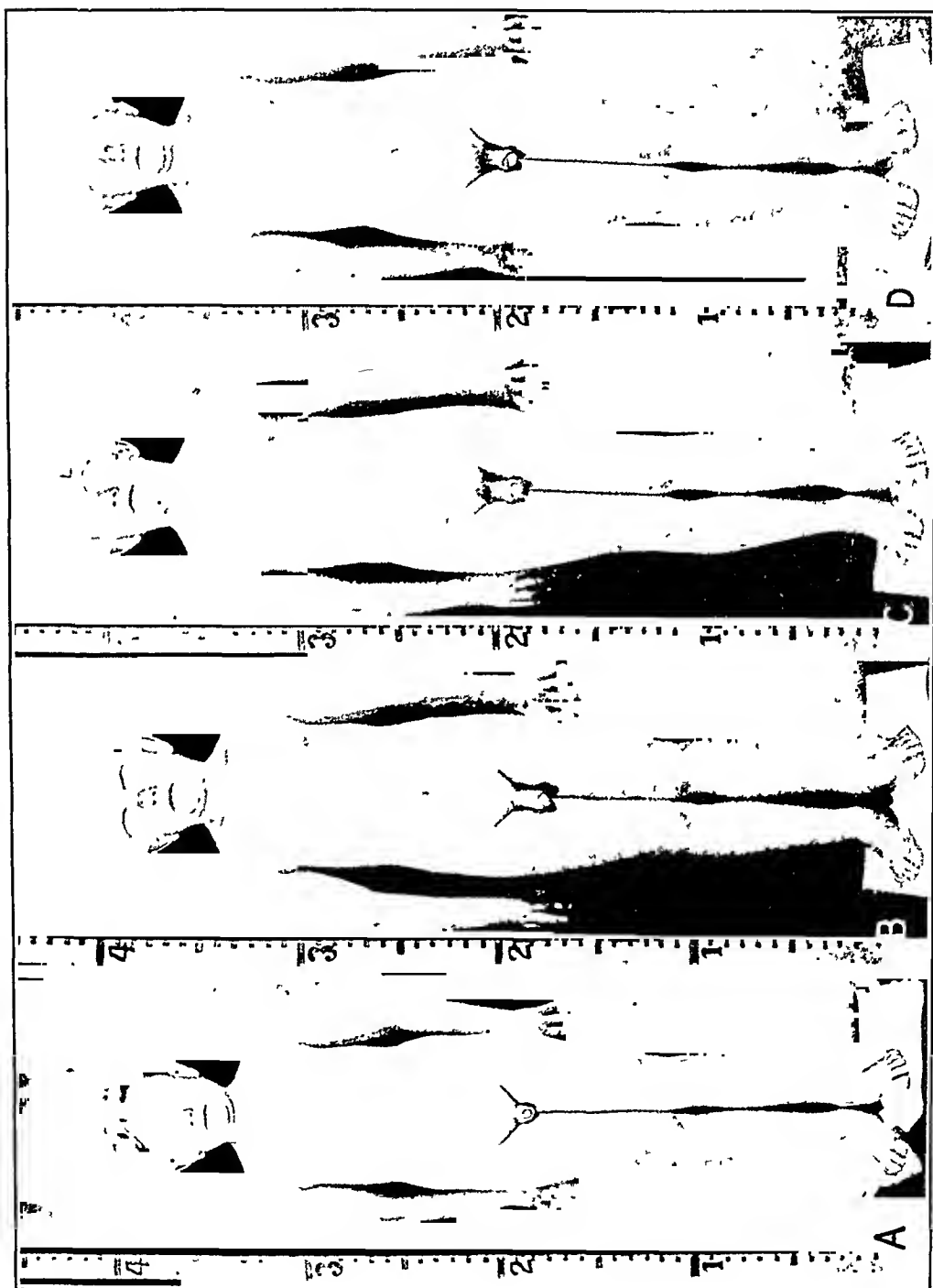
E. S.—2/10/40



E. S.—12/21/39

E. S.—2/10/40

whether testes were found at operation. At 15 he had a course of 23 injections of A.P.L. (500 U. per cc.) with very little effect on genitals or hair growth. His complaints were the usual: lack of growth of penis, girdle obesity, enlarged breasts, high pitched voice, lack of supra-pubic, axillary and facial hair, complete absence of the normal sexual feeling. His weight was 135 pounds, his skin smooth, voice high pitched, breasts prominent,



M. E.—10/1/39

M. E.—12/9/39

M. E.—10/3/40

M. E. 5/7/40

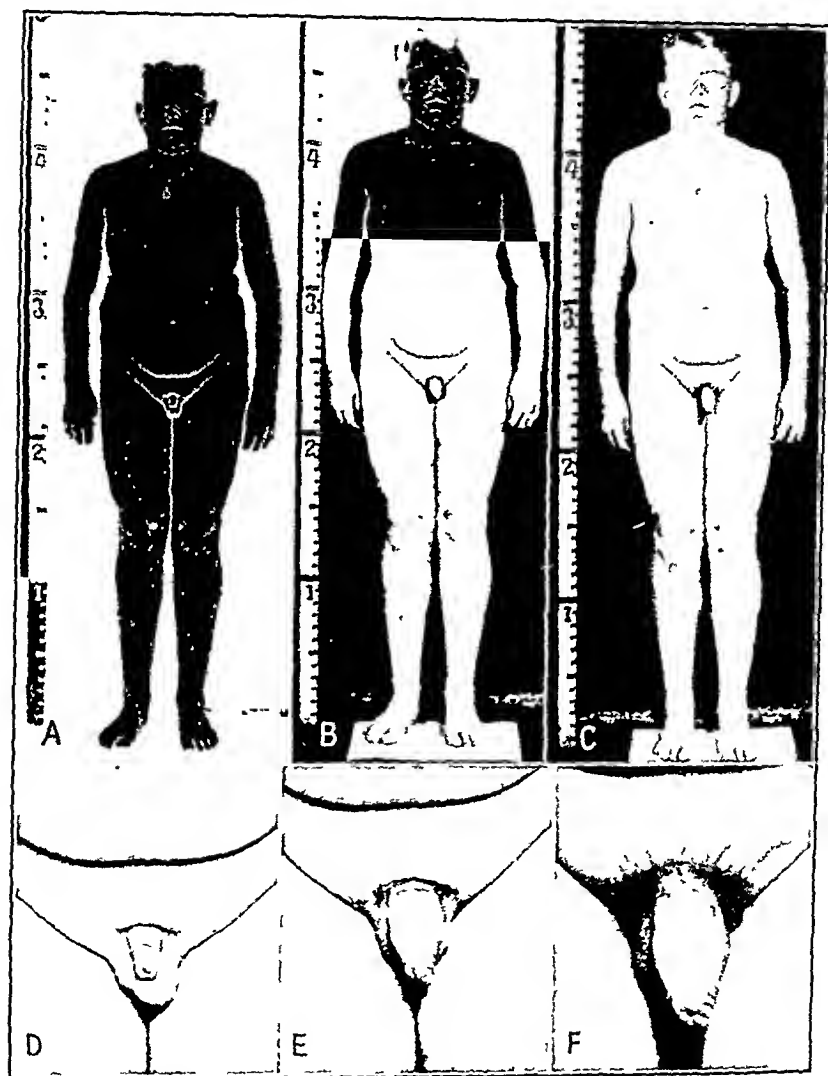
and genitalia very small. No testes could be felt. Examination of heart and lungs were negative. Blood pressure 122/72. His height was 64 inches, span 68 inches, lower measurement (superior symphysis pubis to floor) $35\frac{1}{4}$ inches, upper (superior symphysis pubis to vertex) $28\frac{3}{4}$ inches. Roentgen ray

C. B.—10/15/39

C. B.—6/3/40

C. B.—8/6/40

March 1, 1940, also as above



C. B.—10/15/39

C. B.—6/3/40

C. B.—8/6/40

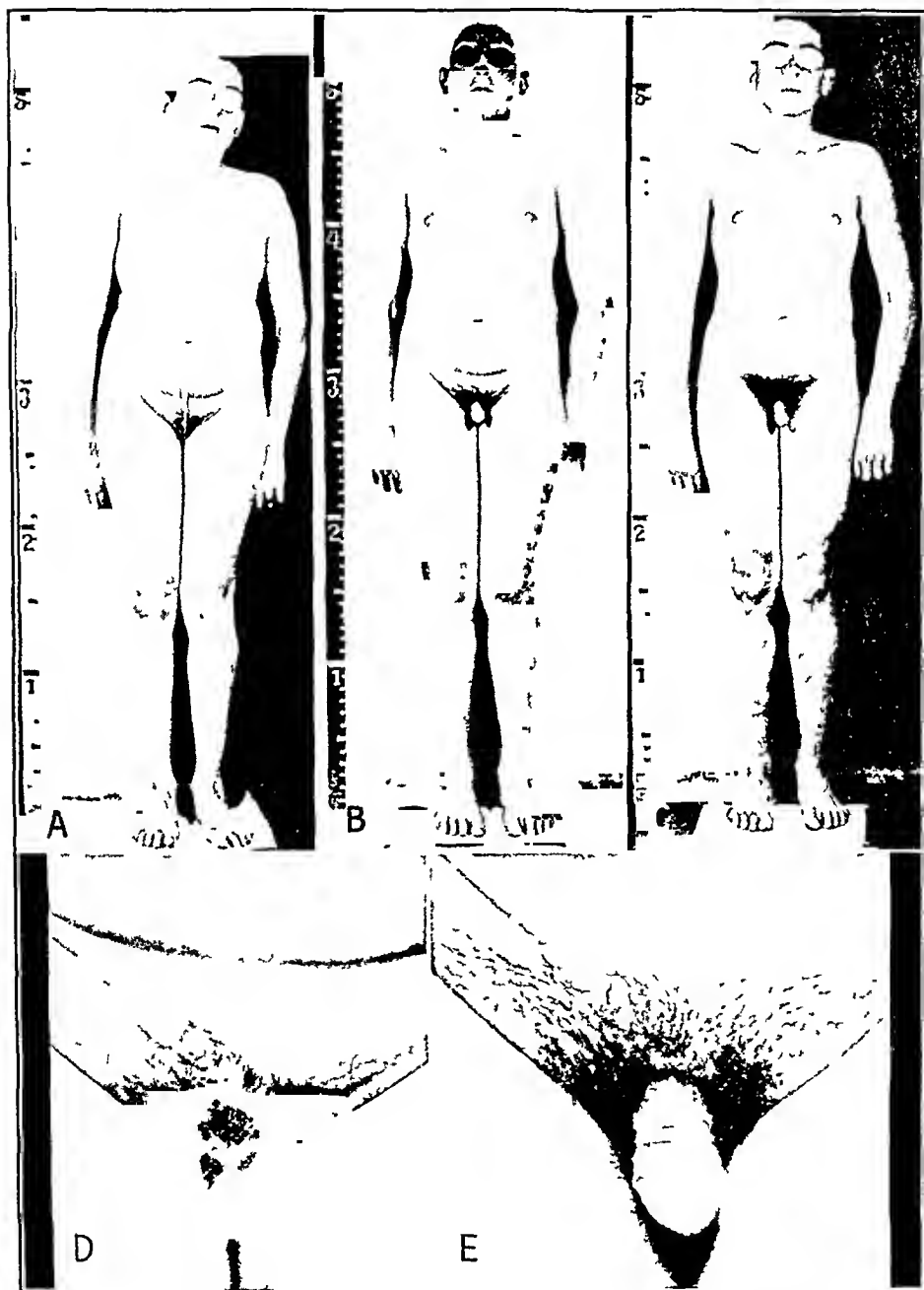
examination of wrists showed normal epiphyseal development for his age. From February 23, 1940, to June 9, 1940, he received 150 mg. methyl testosterone per day, and from June 7, 1940, to September 7, 1940, 100 mg. per day. The changes have been marked and dramatic—growth in size of genitalia, growth in supra-pubic, axillary, and facial hair (he shaves twice

each week, which is an unusual observation or result), numerous and frequent erections, voice is now deep and masculine, increase in stature and change in body configuration.

S. B.—3/1/40

S. B.—5/18/40

S. B.—8/16/40

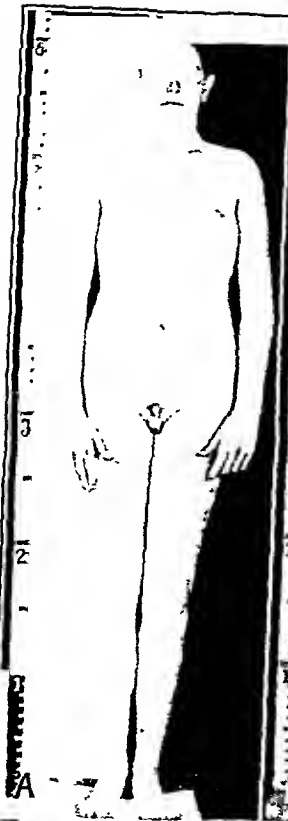


S. B.—3/1/40

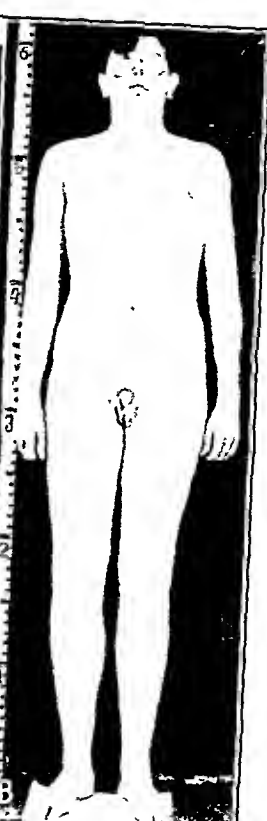
S. B.—5/18/40

CASE 5.—T. McG., aged 22, admitted on December 1, 1939. His family and previous history apparently is without significance. He complained of an awareness of genital underdevelopment and inadequate secondary sex

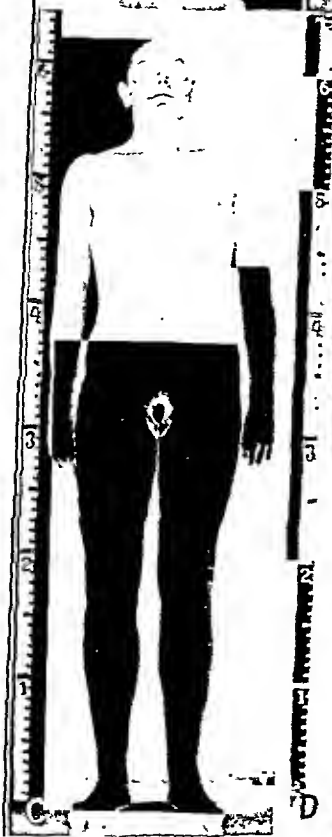
T. McG.
1/2/40



T. McG.
2/8/40



T. McG.
5/24/40



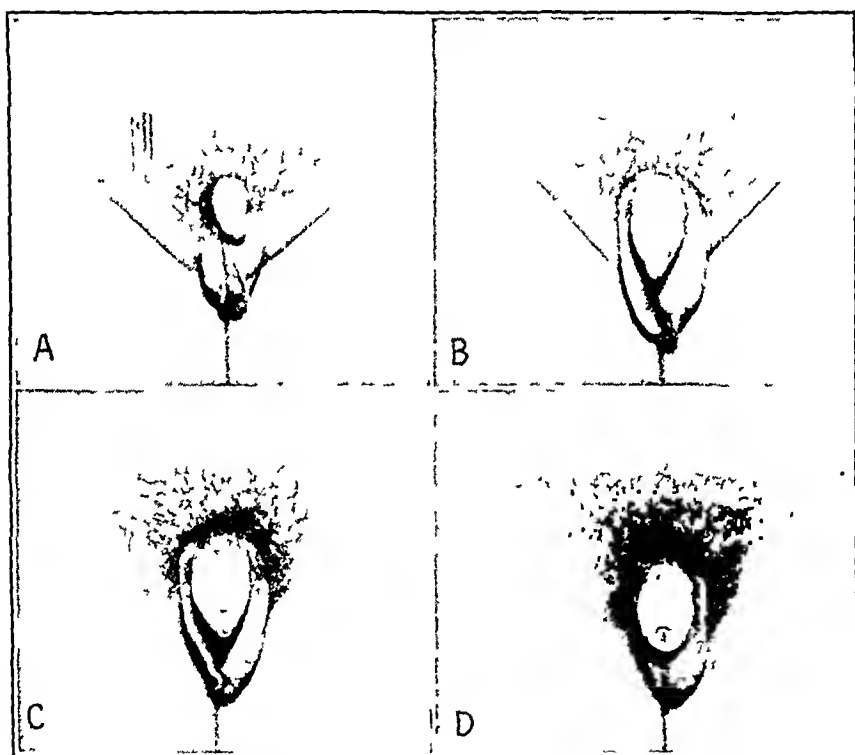
T. McG.
10/3/40



characteristics, since the age of 16, when contact with other boys brought this to his attention. There was a slight amount of libido, and an occasional erection. He was a tall, moderately obese boy with long lower extremities, Height was $71\frac{3}{4}$ inches, span 74 inches, lower measurement 40 inches, upper $31\frac{3}{4}$ inches. Weight was 180 pounds. Slight divergent strabismus. Heart and lungs were normal. Blood pressure 120/65. Slight gynecomastia. There was no facial, nor axillary hair, and a few supra-pubic. Penis was very small, and scrotum small and thin. Right testicle was not felt, while the left was "lima bean" in size. The Roentgen ray photographs of the sella turcica was normal, while the wrists showed delayed bone development, and the epiphyses were open. The basal metabolic rate was -13% . Sugar tolerance curve: 1 hour, 70; 2 hours, 90; 3 hours, 80. On January 6,

T. McG.—1/2/40

T. McG.—2/8/40



T. McG.—5/24/40

T. McG.—10/3/40

1940, treatment with methyl testosterone was commenced, 50 mg. three times daily, by mouth. Within 2 weeks, the penis was larger, reddened, and erections more frequent. The progression was steady, continued and marked—growth of penis and scrotum, left testicle larger, marked growth of supra-pubic and axillary hair, general configuration and appearance more mature and masculine. He gained 10 pounds in weight. There was marked libido and frequent erections. From February 1, 1940, to March 1, 1940, he had edema of the extremities, which was unexplained, excepting as possibly a testosterone effect.

Summary and Conclusion. Methyl testosterone, administered by mouth, 100 to 150 mg. per day, was beyond all doubt effective in inducing testosterone effects in several different types of patients, all

with hypogonadism. Its continued use maintained the effects of testosterone administration. In general, it appears that the earlier changes may be brought about more rapidly by injections of testosterone propionate. All the observations originally made following injections of testosterone propionate in such cases were found in this group with oral administration. Further observations, time, and individual case variations will determine dosage, duration of therapy, regression following discontinuance, and unusual or toxic responses. We feel that toxic or unusual responses are minimal, as are those of testosterone therapy in general. None of the patients complained of gastric distress or upsets. The time of dosage or its relation to meals apparently made little, or no difference. The extremes in variation of response may be due to individual case variations or require further study in dose. Methyl testosterone orally appears to be a good, safe, substitutive form of male sex hormone therapy.

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THE SCOPE OF ARTIFICIAL IMPREGNATION IN THE BARREN MARRIAGE.

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THE involuntarily barren marriage continues, as it has for ages, to present an important medical, economic, and psychologic problem. The oft-quoted statement that from 10% to 15% of marriages in the United States are involuntarily barren, while coldly accurate, does not sufficiently express the appalling degree of marital insecurity and the deep unhappiness which lie submerged in the statistics. It is, therefore, the duty of any physician consulted by a barren couple to appreciate the complexity of the situation and to bend his every effort to the solution of the difficulty. From the standpoint of the required systematic survey, it is essential that *both* partners be assiduously investigated for possible etiologic factors and that any possible impediment, however slight, be removed. The methods of making an organized search in each marital partner and the means of treatment, having been clearly described in recent years,^{7,8} are not within the province of the present essay.

This presentation is concerned with the relatively small group of childless couples who, having been thoroughly studied and, perhaps, treated, find themselves in the unhappy estate of unilateral barrenness—a dilemma in which the female is theoretically fertile

and the male alone is absolutely sterile. Is it the privilege of such unblest women, lucklessly mated to sterile husbands, to achieve maternity artificially? The moral and legal aspects of this question are, for the present, difficult to crystallize, but from the physiologic viewpoint the response is unequivocally affirmative. It must, nevertheless, be admitted that it is well-nigh impossible to apply the medical answer without due consideration to the two imponderable components of the question.

If an absolutely irremediable barrier to fertilization is found in the husband and if the wife, after complete study, is potentially fertile, it is then incumbent upon the physician to explain the hapless predicament to the barren couple. The physician should not attempt to sway the judgment of the couple but should merely discuss with them the need of adjusting their marital philosophy to that of a childless union; or, if they so please, the advisability of adopting one or more children. Occasionally, it will be suggested by one of the partners that the wife submit to artificial impregnation or, as the lay magazines state, "have a test-tube baby." The physician need assume no particular responsibility if one of the first two courses is chosen, but his burden is, indeed, heavy should the couple elect the last-mentioned procedure.

The occurrence of normal pregnancy following the artificial transfer of semen to the reproductive tract of the female is not a newly discovered phenomenon. The fourteenth-century legend of the warring Arabian tribesmen who, in the dead of night, successfully inseminated the well-bred mares of their enemies with semen obtained from inferior stallions is often related as the origin of the procedure. The first successful experimental fecundations were those of Jacobi who, in 1700, was able to fertilize artificially the eggs of fish.⁴ Nearly a century later, the Abbé Spallanzani succeeded in artificially impregnating a spaniel bitch.¹¹ The first successful artificial impregnation in a human female is credited by Home⁶ to John Hunter who allegedly related the occurrence of such a pregnancy following the transfer to the vagina of semen from a husband with hypospadias. In the United States, Marion Sims was the first to employ this modality in sterility. In 1866, Sims¹⁰ reported that 1 of 6 intrauterine inseminations had been successful. Since that time, as reviewed recently by Cary,² many gynecologists have recorded their experiences with artificial impregnation. The procedure is currently in the limelight because of the keener interest in barren marriages and because, as knowledge concerning the menstrual cycle and ovulation accumulates, such inseminations are more often successful. The recent questionnaire survey^{9b} of 30,000 physicians, conducted by the National Research Foundation for Eugenic Alleviation of Sterility, shows that at least 9000 live children were produced by artificial impregnation in this country up to June, 1940.

Indications for Artificial Impregnation. The indications for artificial impregnation in instances of sterility, though limited and well defined, vary with the type of insemination to be employed. The procedure may be either *homologous*, when the husband's semen is artificially transferred to his wife's reproductive tract, or *heterologous*, when the semen of a stranger is employed.

Homologous insemination is indicated in the presence of either penile or vaginal malformations which prevent the normal deposition of semen in a couple otherwise potentially fertile. Thus, either hypospadias or pronounced vaginal atresia may constitute an indication for homologous insemination. A persistently acid reaction of the cervical mucus, as described by Guttmacher and Shettles,⁵ may be considered an indication for homologous insemination of the intrauterine type. The procedure is, however, of no value in the management of ordinary sterility wherein one attempts, as Guttmacher⁴ states, "to give the spermatozoa a 3-inch boost on their 6-inch journey."

Heterologous insemination, utilizing the semen of a donor, is indicated when it has been positively determined that the husband is absolutely sterile, as in either total aspermia or irreparable azoöspemia, and that the wife is potentially fertile. The latter statement implies definite knowledge that the Fallopian tubes of the wife are normally patent, that there is no cervical infection, and that the uterus is not underdeveloped. It is obviously important that the wife be free from any constitutional or local disorder which would make pregnancy hazardous. Heterologous insemination is the type usually employed, because absolute sterility of the male is more common than genital malformations of either partner. For this reason, certain prerequisites to its success, as well as the technique, are herein discussed.

Moral and Legal Aspects of Heterologous Insemination. The conditions imposed upon the physician who consents to perform artificial impregnation in a potentially fertile woman, with semen from a donor other than the husband, include the proper selection of couples in which such a procedure may be risked and the careful choice of a suitable donor.

In selecting the couples, it must be ascertained that both husband and wife are equally earnest in the request that artificial impregnation be performed and that both of them fully grasp the psychologic and emotional dangers which surround such a procedure. It is best to delay the proposed insemination for several months in order that the physician may assure himself that the husband's interest is not abnormally heightened by sheer bravado in an attempt to escape the self-accusations of inferiority. By thus familiarizing himself with the character of the husband, the physician is aided in his determination to avoid any future marital discord.

As a medicolegal safeguard, written permission for the impregnation should be obtained from both partners. The author does not deem it wise or necessary to establish all of the ceremonious legal formalities which Seymour and Koerner^{2a} suggest. Several possible legal charges have been mentioned by both lay and medical writers as constituting serious obstacles, namely, a violation of the law by all concerned, the crime of adultery by the wife, and the aspersion of bastardy on the heir. There being no law, written or unwritten, concerning the legality of the act, the participation by anyone in the execution of artificial impregnation is not a statutory offense. The question of adultery is a debatable one, even though someone has said that "it is difficult to conceive of adultery being consummated in a test-tube." The common law, upon which most decisions concerning adultery would rest, considers adultery to be linked to the concept of sexual intercourse, an element lacking in artificial impregnation. However, as Beardsley¹ points out, the Supreme Court of Ontario, in 1921, sustained a charge of adultery by stating, "The essence of the offense of adultery consists not in the moral turpitude of the act of sexual intercourse, but in the voluntary surrender to another person of the reproductive powers or faculties of the guilty person." If such a decision were generally upheld, it could be made to affect all women who submit to artificial impregnation.

The legitimacy of the child born of artificial impregnation is a delicate question. As a general rule, most statutes protect any child born in wedlock from the aspersion of bastardy. However, even though the presumption of legitimacy is one of the strongest presumptions of the law, it is not absolute under all circumstances. It is easily controverted by proof of the husband's sterility. Therefore, in order to avoid any future shadow of bastardy and to guard the property rights of the child, whose inheritance privileges may be challenged by greedy relatives who by chance acquire knowledge of the manner of conception, it is best to establish protective measures at the time. The suggestion of Seymour and Koerner^{2a} that, after pregnancy results from artificial impregnation, another physician—one ignorant of the origin of the conceptus—be engaged to complete the obstetric care does not solve the problem. The advice of the Legal Bureau of the American Medical Association³ that the husband institute formal adoption proceedings as soon as the child is born, while certainly a safe course, seems to be unnecessarily public. Once a man has accepted a child born to his wife as his own, the law almost guarantees the legitimacy and, therefore, the inheritance of that child. Thus, in the author's opinion, the signed, witnessed consent of both marital partners for the performance of artificial impregnation, to which the husband has appended the affirmation that the child is his and his legal heir,¹ constitutes sufficient legal protection for all concerned.

The selection of a donor entails the impersonal purchase by the

physician of semen from a healthy, fertile male of good character and favorable heredity—one who has no evidence, clinical and serological, of ever having had either gonorrhea or syphilis. The donor must, moreover, be unknown to the barren couple. The request by the couple that a member of the family be employed as the donor should be categorically denied. It is obviously important for esthetic, moral, and psychologic reasons to preserve the anonymity of the donor. It is best that the donor selected be of the same racial strain as the husband and, if at all feasible, possess some of his physical characteristics.

Technique of Artificial Impregnation. The success of any insemination hinges on the potential fertility of the wife, as previously mentioned, on the excellence of the donor's semen, and on the timing of the insemination. The manner of introducing the semen into the vagina is the simplest part of the procedure. The donor is instructed to obtain the semen by manual masturbation, collecting it in a sterile, dry, glass vial and keeping it at room temperature until used. The semen should be introduced into the recipient as soon as possible after its collection, certainly within an hour. The specimen should be examined microscopically, as a check, when it is received from the donor.

The wife is advised to have intercourse with her husband, if he has no pyospermia, just prior to reporting for the insemination, with the hope that an imminent ovulation may be hastened and that favorable cervical secretions will be stimulated. If intercourse with her husband is not feasible, the woman is advised to take a preliminary vaginal douche with 2.5% solution of sodium bicarbonate. *The temporary alkalinity of the vagina thus achieved may enhance the fertilizing ability of the spermatozoa.* With the patient in the usual lithotomy position and the table tilted to the Trendelenburg angle, the specimen of semen is then merely squirted against the external os *without exposing the cervix.* For this purpose, it is convenient to use a sterile, dry, glass syringe and a blunt, 16-gauge needle. The patient is kept on the table in the Trendelenburg position for 30 minutes and is then permitted to follow her customary duties.

There is nothing to be gained, in the author's experience, by introducing the semen directly into the uterine cavity through a small rubber catheter or a Keyes-Ultzmann cannula. In fact, the results of the intrauterine method may be inferior because of the expulsive contractions of the uterus evoked by stimulation of the internal os. It is imperative, when the intrauterine technique is employed, to allow the uterine spasm caused by the passage of the catheter or cannula to subside before introducing no more than 0.5 cc. of the semen. A larger quantity of the semen tends to distend the uterine cavity and may give rise to undesirable contractions.

The timing of the artificial insemination so that it coincides with ovulation is obviously of paramount importance. When the wife is

able, because of either habitual midcycle pain or cyclic expulsion of clear cervical mucus, to foretell accurately the time of ovulation, the problem is simplified. If, however, no signs suggestive of ovulation are available, as is usually the case, 2 or 3 inseminations during the midportion of a single cycle should be performed. When failure occurs, even after such multiple inseminations, the days of the cycle selected should be altered at the next trial. In one of the successful cases herein reported, for instance, pregnancy did not occur after inseminations on the 11th and 14th days of the menstrual cycle but did follow subsequent inseminations on the 12th and 15th days. It is obvious that a large element of chance is involved in the meeting between a highly fertile ovum and a spermatozoön of similar quality. Seymour and Koerner^{9b} recently reported that the average number of inseminations successfully employed by more than 4000 physicians was 12. This number of attempts was distributed in many ways, such as 1 insemination per month for 12 months, 2 inseminations per month for 6 months, and so forth. It is significant that 124 physicians reported successful artificial impregnation after as many as 21 inseminations. The patient, donor, and physician must be prepared, therefore, to repeat the procedure many times before meeting with success. The patient and donor will be more coöperative, if this is explained prior to the undertaking.

The recent observations of Guttmacher and Shettles⁵ on the cyclic penetrability of the cervical mucus to spermatozoa may obviate the necessity of multiple inseminations. These authors recommend the application of a micro-technique for the repeated study of the penetrability of cervical mucus and record several successful inseminations during the so-called optimal phase of maximum spermatozoal penetration. The method described appears to deserve future study and trial.

TABLE 1.—DATA CONCERNING SIX ARTIFICIAL IMPREGNATIONS WHICH RESULTED IN NORMAL INFANTS AT TERM.

Patient.	Age.	Condition of husband's semen.	Number of inseminations.	
			Per menstrual cycle.	Total.
1	28	Azoöstermia	1	1
2	39	Azoöstermia	1	1
3*	31	Aspermia	2	10
4*	32	Aspermia	2	4
5	30	Azoöstermia	2	6
6	28	Azoöstermia	3	9

* The same patient; impregnations performed 18 months apart.

Report of Cases. The author has had the privilege of attempting heterologous artificial impregnation in 6 barren women whose husbands were absolutely sterile (Table 1). Five of the 6 women became pregnant and delivered healthy offspring. One of the 5 was successfully impregnated twice. The number of inseminations

received by these 5 women before pregnancy occurred varied from 1 to 10 (Table 1). The infants delivered, now ranging in age from 2 years to 6 months, are normal in every respect. The remaining patient is still undergoing repeated inseminations and, although 4 pairs of inseminations have been unsuccessful, one may not yet classify this as a failure.

Summary. 1. The legal and moral aspects of artificial impregnation, though not yet clearly defined, are discussed.

2. The history, indications, and technique of artificial impregnation are briefly stated. It is shown that the procedure may be easily accomplished if certain rules concerning the selection of the semen and of the potentially fertile wife are followed.

3. Six successful instances of artificial impregnation are herein recorded.

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OBSERVATIONS ON THE ORAL ADMINISTRATION OF RAG-WEED OIL IN PATIENTS HYPERSENSITIVE TO RAGWEED OIL.

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It has been observed for some time that ether-soluble fractions of various plants were relatively common causes of contact dermatitis. The type of plants causing eruptions have been well recognized in the different geographical areas of this country. The specific management of patients manifesting plant oil dermatitis has not been adequately approached. For this reason further recorded observations in desensitization to plant oils seem justified.

Contact dermatitis treated by specific desensitization is regarded with great skepticism. This view would appear to be based upon

few observations. Jadassohn⁴ described a case of desensitization in mercury idiosyncrasy, Riehl⁷ in arsphenamine dermatitis; Urbach¹⁰ in resorcin and in arsphenamine dermatitis, and Richter⁶ in contact dermatitis of various origin. Blumenthal and Jaffe¹, in a sizable group of contact dermatitis cases, found desensitization unsuccessful except for the oil group. In one patient with multiple plant oil sensitivities these authors found a highly specific desensitization to an oil of lavender.

There is general agreement that contact dermatitis due to oils is the type that offers the best chance for specific desensitization. In this country, Caulfeild,³ Seyler,⁸ Shelmire,⁹ and many others have published favorable results with specific desensitization to plant oils. On the other hand, Brunsting and Williams² express a negative view about the therapeutic value of desensitization, especially in ragweed oil dermatitis.

For the most part, plant oil¹⁰ desensitization has been attempted by hypodermic injection or by external application. Duncan and Dakins, however, are among the few who have tried oil by mouth. These authors recommended chewing the leaves of *Rhus* and swallowing the juices. Perutz⁵ gave turpentine by mouth. According to American Indian folk lore, the early tribes had the habit of chewing the green leaves of plants belonging to the *Rhus Toxicodendrum* group as a means of preventing summer skin eruptions. The literature would infer that this procedure gave good protection to the tribesmen but often resulted in a temporary acute skin eruption and a temporary general debilitation.

Our observations were made in a group of 16 patients, all of whom manifested a typical contact dermatitis. In these cases we tried specific desensitization for the purpose of clearing the individual eruptions and to protect the patient against further attacks. For the most part we dealt with an isolated farmer population. Since under these circumstances regular treatment by hypodermic inoculation proved to be a difficult procedure, we gave the oil by mouth.

The essential details of occupation, patch test results, duration of the eruption, and season of the disease are detailed in Table 1. All of the cases manifested their eruption on the exposed surfaces; in Cases 2, 3 and 5, in addition to the exposed surface, the eruption occurred over both legs from the knees to the ankle, explainable on the basis of contact by walking in hay and fields containing the ragweed plant. Fifteen of the 16 patients had seasonal exacerbations of their eruptions occurring at the time of good development of the ragweed plant and during the season of ragweed pollination. Three of the patients had their eruptions throughout the year but they were always worse from mid-August through September, explainable on the basis of constant contact with hay which contained ragweed plants. All of the patients gave a 4+ positive patch test reaction to oil of ragweed in dilution of 1 to 1000 or higher dilution after

24-hours' exposure. Positive patch tests occurred to other chemical substances but the clinical picture and history in every instance would exclude other substances as being of practical clinical importance.

TABLE 1—CLINICAL DATA IN 14 CASES OF RAGWEED OIL DERMATITIS

Case no	Name	Age	Onset	Season	Site	Occupation	Treatment ragweed oil	Patch test	Results
1	J L	47	42	Chiefly Aug - Sept	Exposed surfaces	Farmer and mechanic	1 gtt D 1/200	4+ 1/1000	Complete relief 3 year
2	H M	60	57	Late Aug	Exposed surfaces	Caretaker on farm	1 gtt D 1/500	4+ 1/200	Summer relief 1936-1937
3	H J	58	55	Start June, early Sept	Exposed surfaces	Mechanic, gardner	Up to 5 gtt D 1/100	4+	Unsatisfactory
4	L G	45	36	Late Aug. to Nov	Exposed surfaces	Truck driver	2 gtt T D	4+ "	Unsatisfactory
5	J A	55	50	Mid-summer mid-winter	Shoetops to knees	Farmer	5 gtt D 1/100	4+	Fair
6	C W	51	47	Entire year worse in summer	Shoetops to knees	Farmer	1 gtt D 1/10,000	Alfalfa oil 4+	Fair
7	C H	73	60	Entire year worse in summer	Exposed surfaces	Farmer	1 gtt D 1/10,000	4+ 1/10,000	Complete relief 2 years
8	L M	29	27	July to Nov	Exposed surfaces	Unemployed	1 gtt D 1/100,000	4+ 1/100,000	Complete relief 3 years
9	R C	54	48	Aug to Nov	Exposed surfaces	Farmer	1 gtt D 1/100,000	4+ 1/1,000,000	One season good
10	W G	41	37	Entire summer	Exposed surfaces	Lives in field	1 gtt D 1/400	4+ 1/1000	One season complete relief
11	J H	53	51	Aug to Sept	Exposed surfaces	Factory	1 gtt D 1/10,000	4+ 1/10,000	Four years satisfactory relief
12	J M	46	44	July to Nov	Exposed surfaces	Farmer	1 gtt D 1/20,000		One season complete relief
13	A T	65	58	July to Aug, mild all year	Exposed surfaces	Farmer	1 gtt D 1/200	4+	One season complete relief
14	E W	56	53	July to Nov	Exposed surfaces	Miner	1 gtt D 1/10 000	4+ 1/10,000	One season complete relief

Preparation of Materials. The ether soluble residue of the ragweed plant used for diagnostic and therapeutic purposes in this study was prepared in the following manner: Fresh, healthy giant and dwarf ragweed plants were collected in early September. The plant was allowed to dry and the stems and leaves were then ground to a fine powder, an excess of commercial ether was added and placed in a tightly stoppered bottle. This mixture was allowed to extract at room temperature for the next 48 hours. The ether was allowed to

evaporate. The residue was warmed and diluted in serial dilutions of ten, with warm olive oil.

Method of Treatment. All of the patients were patch-tested with oil of ragweed in olive oil in dilutions 1 to 100, 1000, 10,000, 100,000, 1,000,000. Treatment was begun with the drop of a dilution which gave a faintly positive 24-hour patch-test reaction. The oil was dropped on a teaspoonful of sugar by a non-ragweed oil sensitive person and taken by the patient each morning before breakfast. The chart further lists the doses of ragweed oil, the duration of treatment and the results obtained. Emphasis is placed upon the variability of the dosage. This has depended upon the degree of skin hypersensitiveness of the individual patient to ragweed oil.

Discussion. We wish to emphasize that the dosage of ragweed oil administration depends upon the patch-test reaction. It is recommended that all patients start with one drop of a strength solution which gives the faintest possible positive 24-hour patch-test reaction. In Cases 1, 2, and 3, administration of 1 drop of ragweed oil in 99 parts of olive oil on 2 successive mornings produced a generalized eruption characteristically similar to the eruption of external application of the oil. Repeating the same dosage following complete clearing of the eruption resulted in a second exacerbation in all 3 of the patients. They were, however, able to tolerate a dosage of 1 drop of 1 to 10,000 dilution which gave them complete protection from their usual daily exposure.

The fact that all of our patients gave a good positive patch-test reaction to oil of ragweed pollen makes it understandable why our patients have their eruption only during the pollen season or are worse during the period of pollination of the ragweed plant.

By repeated quantitative patch testing we have observed a reduction in the quantitative patch-test reaction in Cases 1 and 2. Before treatment, they reacted positively in dilutions 1 to 100,000, and after 2 years of continuous treatment they reacted only in dilutions of 1 to 1,000 in Case 1, and 1 to 200 in Case 2. In 5 others (Cases 3, 5, 6, 7, 10) there has not been a quantitative reduction in the patch test but in spite of this fact they are symptom-free.

Twelve of the 16 ragweed oil sensitive patients have been satisfactorily controlled with oral desensitization to ragweed oil. Two of the failures have not followed treatment sufficiently to justify an evaluation of therapy. We are unable satisfactorily to explain the failure in the other 2 patients.

Patients 3 and 4 were treated while they were in an exacerbation (September) with no appreciable benefit, suggesting that long continued treatment is necessary for a good therapeutic result.

Conclusions. 1. Sixteen patients with contact dermatitis due to hypersensitiveness to oil of ragweed were treated by oral administration of ragweed oil; 12 experienced satisfactory results.

2. It would appear that actual desensitization can be accom-

plished in plant oil contact dermatitis by oral administration of the specific oil.

3. Oral administration of oil of ragweed in greater than tolerance dose results in a generalized eruption of the contact type. Involvement, however, is maximum at the site of the previously involved areas.

4. Oral treatment with ragweed oil must be daily and continuous over long periods of time.

5. Oral desensitization to ragweed oil is recommended when there is a long intervening period before the expected time of contact with the plant or its pollen.

6. The therapeutic dose and overdose of ragweed oil are in close proximity. The estimated therapeutic dose, therefore, can best be determined by quantitative patch tests.

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CLINICAL INVESTIGATIONS WITH CURARE IN ORGANIC NEUROLOGIC DISORDERS.*

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CURARE, known to South American Indians for generations, has been known to medical science for only about 100 years. Since time immemorial, the native Indians have used small amounts of gum curare upon arrow tips to paralyze game in hunting. Generalized muscular paralysis and respiratory death occur within a few minutes after injection of curare into the animal. The secrets of curare preparation have been carefully guarded and much "black magic" obscures its manufacture.

Now and then small amounts of the crude drug have been brought back to civilization since the time of Raleigh. In 1815, Watterton and Brodie demonstrated asphyxia to be the cause of death. Baussingault and Roulin in 1824, extracted the alkaloid curarin. In 1844, Schomburgh named the plant group *Strychnos toxifera*.

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In 1844, Claude Bernard first described the physiologic action of the drug upon the neuromuscular junction and confirmed asphyxia as the cause of death. Others contributing to our knowledge are Preyer, who, in 1864, isolated curarin in crystalline form; Pelouse and Lapique, who reported physiologic observations confirming the pure myoneural action of the drug.

Jousset, Demine and Busch in 1867, first attempted to apply the drug to clinical medical therapy. They treated convulsive states, epilepsy, rabies, chorea, strychnine poisoning, and various tics. Hoffman (1879), Höch (1894), and Cash (1901), also experimented with curare. Tsocanakis, in 1924, tried curare in spastic paralysis. Bremer³, in 1929, proved that the drug exhibited a selective action in reduction of local tetanus and decerebrate rigidity. West⁷ (1931-35) and Cole (1934) reported partial results in the relief of tetanus convulsions, rigidity of Parkinsonism causalgia, and spastic paraplegia. Burman⁴ (1938-39) reported extensively upon its relaxing effect, in spastic, athetoid, and dystonic states of muscular rigidity and tremor.

A great drawback to experimental and clinical investigation of the drug has been the fact that no gourd or tube of crude curare made by one witch doctor would duplicate the ingredients of another, together with inaccurate information from native curare makers. Also, different curare plants from various areas give varying toxic action. Other lethal substances such as venom were added from time to time; these contaminants have snarled chemical and physiologic research. On the whole, pharmacologic literature gives the impression that the drug is highly toxic and dangerous, not applicable to clinical medicine. Furthermore, until recently, no large quantities of authenticated curare have been available at any one time for experimental research.

In 1934 Mr. Richard C. Gill⁵, after exhaustive studies and prolonged contact with South American Indians, was able to learn the actual botanical ingredients and the secrets of manufacture. In 1938, he brought back to this country the largest amount of authentic and field-tested curare ever gathered and carried back to the civilized world. In addition, he returned with a large amount of unauthenticated curare, that is, curare from regions he had not personally visited. This supply was turned over to the E. R. Squibb and Sons' research department.

Standardization of the Drug. After considerable independent experimentation by Dr. A. R. McIntyre, Professor of Pharmacology at the University of Nebraska, and by Mr. H. A. Holaday, head of the biologic development and control division of Squibb and Sons'* biologic laboratories, the technique of standardization, at first difficult, has been simplified. Biologic methods of assay are neces-

* I am indebted to E. R. Squibb & Sons and Dr. Sidney Newcomer for furnishing standardized curare (Intocostrin) in these experiments.

sary with each new batch of the drug. The curare itself is extraordinarily stable, not destroyed by autoclaving. Assay by a variety of methods gives a result so precise that recheck reveals an error within the limit of 1%.

Methods of Assay. Curare-acetylcholine antagonism upon a frog gastrocnemius preparation has been applied in the study of methods of purification and in dilution control. A frog gastrocnemius preparation is made which, with addition of acetylcholine, produces an isometric type of contraction which furnishes a reference height for comparisons with a decreased height contraction obtained through the inhibiting effect of the curare solution. The method is applicable only when controlled by a reference standard qualitatively identical with the test material.

Another method of assay is the head-drop method in the rabbit, developed by Holaday. The curare solution is injected slowly into the ear vein of the rabbit and the dose adjusted so that the neck muscles after $2\frac{1}{2}$ to 3 minutes reach a degree of flaccidity which just prevents the animal from raising the head and keeps the chin down. This end point is very clear cut and a typical curare effect occurs exactly as seen in the human after injection of a curarizing dose. The amount per kilogram necessary to produce this effect in the rabbit is estimated and the dosage is figured according to body weight of the patient.

Physiologic Action of Curare. Action of pure curare is upon the neuromuscular mechanism. In certain impure preparations, another action is seen, ascribed by Burman to curarin. This side-effect is a histamine-like action producing sudden fall in blood pressure, bronchial spasm, facial pallor, erythema, and urticaria, which is relieved by epinephrine. These preparations we have not employed clinically but are investigating them further. We believe them unsafe for clinical use.

The action of curare is upon the net-like structure of fine nerve fibers at the terminus, called the motor end plate. It is here that acetylcholine, the chemical mediator or regulator of chronaxie of nerve impulses to voluntary muscle, acts. Curare prevents acetylcholine from acting on the nerve muscle junction and inhibits its action, thus producing a paresis of muscle. Curare poisoning (curarization) thus prevents the transmission of natural nerve impulses from motor nerves to the muscles. This peripheral motor flaccid paralysis affects, in general, the nerve endings of all striated or voluntary musculature, but selectively affects, first, the fine fast moving muscles of high chronaxie, such as short muscles of the eyes and throat; later, the larger, slower moving muscles of head, neck, extremities, intercostals, and diaphragm.

The circulation is relatively unaffected and sensory nerves are not affected. While reflexes may be somewhat diminished they are not abolished. Death occurs from asphyxia due to respiratory paralysis.

The so-called lethal point of the drug is questionable because large doses are tolerated if respiration can be continued. The drug is quick acting and very rapidly eliminated. The rapidity of absorption has much to do with lethality. Small amounts of the drug injected rapidly are toxic and produce cardiac failure in animals while large amounts may be given slowly without toxic symptoms. Fifty times the lethal dose has been given to dogs by Dr. A. R. McIntyre without fatality by keeping up artificial respiration.

The physiologic effects are noted immediately at the end of an intravenous injection given over a period of 1 to 2 minutes. In about 2 more minutes the peak of curarization is reached, whereupon the effect slowly recedes and seems to vanish in 15 to 20 minutes. The same effect occurs in from 15 to 30 minutes after intramuscular injection. Physiologic symptoms are seen in the following sequences: The patient first complains of haziness or fuzziness of vision. Next, bilateral ptosis appears with slight nystagmoid movements, relaxation of the face and heaviness, with relaxation of the tongue and jaws. The patient at this point complains of tightness of the throat and huskiness of the voice. Generalized heaviness and weakness of the neck muscles with inability to raise the head are followed by weakness to complete paresis of the spinal muscles, legs and arms. Last, appears shallowness of respiration from weakness of the intercostals and the diaphragm.

These symptoms follow the same order as the progressive symptoms of a patient with myasthenia gravis; double ptosis and nasal smile also simulate those of the myasthenic. Excess saliva may accumulate in the throat and the patient complain of difficulty in breathing, but this occurrence is counteracted considerably if the relaxed jaws and tongue are held forward. Injections of epinephrine, prostigmin, or metrazol all seem to counteract quickly the action of curare. Burman believes that a sustained, clinically relaxing effect upon hyperkinetic or spastic muscles remains for a long period of time after the toxic deacetylcholinizing effect of curare has disappeared. We have not yet been convinced of any such prolonged action from curare. In fact, its usefulness is hindered by this temporary effect in spastic states. The only evidence we have for a possible prolonged action is the fact that a second intravenous injection in animals, if administered within 1 to 5 hours after an initial dose, will be more effective (depending upon the time interval), so that less curare is required to cause paralysis. In giving a second intravenous injection to patients after complete curarization seems to have disappeared, we have also noted it takes a lesser amount of curare to produce paralysis. The observation indicates that there is considerable prolongation of effect or retention of active alkaloid.

There are a number of drugs known to have a curare-like action: Quinine methochloride, erythroidine hydrochloride, ammonium

bases, amides and amines, choline, muscarin, snake venoms, methylstrychnine, aromatic series, pyridin, quinolin, thallin, nicotine series, piperidin, putrefactive ptomains, and products of muscular metabolism. References to the action of these drugs can be found in pharmacologic literature. One will be discussed later in this paper.

After extensive experience with curare, I¹ developed a method of preliminary curarization of the patient prior to metrazol convulsive shock therapy which has completely removed all traumatic hazards of that treatment. The technique of this therapy has been described elsewhere.

Some clinical neurologic disorders resemble curare poisoning. Botulism, the food poisoning from improperly sterilized canned foods, produces a peripheral motor paralysis with respiratory failure resembling curarization. Acute ascending Landry's paralysis, often erroneously called acute poliomyelitis, is in reality an obscure toxic condition with an almost pure peripheral motor paralysis progressing until all voluntary musculature is involved, ending in respiratory paralysis and death from asphyxia. Myasthenia gravis, as noted earlier, in the progression of symptoms with its characteristic rapid fatigue of muscle from faulty function of the neuromuscular junction due to loss of acetylcholine, resembles mild curare poisoning. Both curare poisoning and myasthenia symptoms are immediately relieved by prostigmin.

Clinical Application of the Drug. The use of curare in clinical medicine must still be regarded as experimental. A large amount of investigative pharmacologic research and clinical experimentation must be carried out before curare can find a useful place in medical therapeutics. Yet, there is a tremendous potential usefulness for a safe drug with a curare-like action. The results from curare therapy up to the present have been inconclusive, owing to the fact that adequate supplies of standardized material have been almost impossible to obtain. This problem has now been overcome and the drug has proved to be indispensable in preventing complications of convulsive shock therapy.

In the field of neurology curare may find its greatest usefulness. West has reported interesting results with curare in the treatment of tetanus. In lockjaw, the violent muscular contractions become almost constant tetanic convulsions, finally exhausting the patient and ending in death. The recognized but not too effectual treatment is tetanus antitoxin. Greatly needed is a method of continuously relaxing the muscular spasms until the patient can develop an immunity against the toxin of tetanus bacilli. Curare, theoretically, offers such hope of preventing exhaustion, by relaxing the muscular spasms and producing a generalized peripheral muscular paresis.

The drug may also prove useful in controlling other convulsive states such as strychnine poisoning, eclampsia hydrophobia, and

status epilepticus. It should be possible to suppress these spasmodic disorders by sustained "physiologic" doses of curare. In well chosen cases a slow acting curare would be life saving as continued convulsions heighten fatigue. Even near-lethal doses might be administered with the aid of artificial respiration by means of a respirator. Certainly, experimentation with curare is worthy of trial in any convulsive disorder that is endangering life.

A most promising field for a curare-like drug is in the so-called spastic paralytic states. Infantile cerebral palsies, spastic paralysis, or Little's disease, usually the result of birth accidents, are responsible for one of the largest groups of cripples. No medical treatment has been previously known for these disorders. Orthopedic treatment, surgery, and physiotherapy for muscle training have been all that could be offered. Curare releases the spasm and muscle rigidity and involuntary tremor and spasms disappear through relaxation. While these effects are not curative, the transient relaxing effect enables the paralytic patient to talk better, use the hands for finer movements such as feeding, writing, and so on, and permits relaxation of the limbs. Such added benefit enables the orthopedic surgeon to use braces more effectively and to carry out necessary surgery of fixed deformities. The problem is to get a drug with a prolonged action. At present curare action is too fleeting; a slow sustained effect is essential. After obtaining the drug effect, there is still the problem of muscle reëducation through physiotherapy exercise to learn new control of formerly helpless muscles. The child is able to gain faster as a result of the relaxing effect of curare. Much investigative research is necessary before this treatment can be successfully applied.

There are a number of other organic neurologic diseases characterized by rigidity of muscles and involuntary spasms and tremors from involvement of lower motor centers of the brain in the basal ganglia or striate system. Some of these are paralysis agitans, athetoid disorders, dystonia musculorum deformans, lenticular degeneration, multiple sclerosis, postencephalitic Parkinsonism and oculogyric crises, Huntington's chorea, spasmodic torticollis, and hemiballismus. These are all disabling conditions and notoriously resistant to treatment. Small doses of curare cause a diminution in the hypertonia, tremor, and involuntary motility of these disorders, thus giving the patient marked temporary relief. Even though its use is not curative, it would enable the patient to live a life of comparative comfort. Here again, a slow-acting, sustained effect is necessary if the drug is to become a useful therapeutic aid.

Personal Experiences. 1. *Spastic paralysis.* A group of 12 severe cases of spastic paralysis were given curare injections every other day, 10 mg. per 20 pounds of body weight, for a period of 3 to 8 months. Each child was accepted for treatment from a large number of spastic cases because of some unusual or different symptom.

Eight of these children were under constant supervision at the Nebraska Orthopedic Hospital. Orthopedic procedures and physiotherapy were carried out at the same time. The following cases are examples of the results obtained:

Case Reports. CASE 1.—E. B., aged 9, was the first child subjected to treatment because of the severity of the condition—a marked spastic tetraplegia with severe contractures of all extremities; incoördination and dysarthria were present. An attempt to release the contractures by casts had resulted in severe pressure ulcers and violent exhausting spasmodic contractions. All surgical attempts were unsuccessful; sedative drugs were likewise ineffectual. Curare therapy carried out over an 8-month period produced a marked improvement, enabling the patient to tolerate plaster casts and extension procedures to overcome fixed deformities.

CASE 2.—R. M., aged 12, with severe spastic tetraplegia and marked athetosis and dysarthria, was unable to stand or feed herself. Curare treatment was directed toward improving the athetosis. This child was on treatment for 5 months. Slow but constant progress resulted in the child's becoming able to walk and feed herself. More rapid gain from physiotherapy was seen as a result of curare.

CASE 3.—E. P., aged 18, had a severe spastic tetraplegia with marked involvement of the upper extremities, pronation contractures, athetosis, and dysarthria. Curare treatment was directed toward improving function of the arms and speech function. A 4-month treatment was carried out, but only transient, temporary improvement was noted in speech function and lessening of the athetosis.

CASE 4.—A. P., aged 8, had severe spastic tetraplegia with contractures of all extremities, athetosis, dysarthria; he was unable to sit alone. Curare treatment directed toward relaxing spastic contractures and incoördination of the arms was carried out for 3 months. While a transient, temporary relaxing effect was noted no permanent gain occurred.

CASE 5.—B. F., aged 7, had spastic tetraplegia with marked incoördination, dysarthria, and spastic contractures. Curare treatment, directed toward improving coördination and relaxing spasticity, was given over a 3-month period. The result was a slow, but sustained improvement, hardly attributable to curare since its effect was too transient.

CASE 6.—B. L., aged 16, had spastic tetraplegia with dysarthria, spasmodic torticollis, athetosis, and spastic contractures. Curare treatment, directed toward spasmodic torticollis and athetosis, was given over a 4-month period. The result was temporary improvement after each injection, but again the curare effect was too transient and fleeting.

CASE 7.—R. L., aged 12, had spastic tetraplegia with dysarthria, facial grimacing, mental retardation, and inability to hold up the head. Curare treatment directed toward the speech defect and grimacing was given over a period of 1 month, but was discontinued because of the hopeless prognosis.

1. *Comment on the Entire Group.* Curare produces a definitely but transient, relaxing effect upon spasticity without fixed deformity. It reduces incoördination, athetosis, and dysarthria. Favorable progress occurred in the majority of the patients while under curare therapy. The treatment is not dangerous and there are no toxic reactions.

A sustained curarization would be a valuable aid in the treatment of spastic paralysis and extra pyramidal rigidity states.

Five adult patients with spastic paraplegia caused by such diseases

as transverse myelitis and advanced multiple sclerosis have been given curare treatment. The drug will temporarily relax these spastic contractures but its effect is transient. It does, however, give patients relief from painful spasm and for this purpose alone can be recommended.

2. *Status Epilepticus*. We have had opportunity to study the effect of curare upon one case of status epilepticus. In a child with an obscure infection there developed toxic encephalitic symptoms with hyperthermia, a syndrome of decerebrate rigidity, spasmodic myoclonus with grand mal seizures that occurred every few minutes. These seizures were uncontrolled by various sedative drugs and ether anesthesia over a 10-day period. At the time curare was given, the child was moribund. Continuous intravenous curare injection was kept up for 12 hours. During this period the patient was completely relaxed and free of seizures and rigidity. The child died, apparently of cardiac failure, but necropsy examination was refused.

3. *Parkinsonian Syndrome and Paralysis Agitans*. Six patients with both encephalitic Parkinsonism, oculogyric crises, and paralysis agitans have been given curarizing doses of curare. The rigidity relaxes, tremor and oculogyric crises disappear, but as the effects of the drug wear off in about 1 hour, the former rigidity and tremor return. During this period the patient is unable to carry out active movements and complains of weakness. We see no advantage from the relaxation under curare over that obtained from belladonna-derivative antispasmodic drugs which can be given by mouth.

4. *Huntington's Chorea*. I have never observed any relief of involuntary movements of hereditary chorea from previous drug therapy. To 1 patient in private practice and 3 patients in a state hospital, I have given repeated physiologic curare injections. The incoördinate movements cease while curarization is present and slowly return to their former state within a few hours. These patients express gratitude for the relaxation obtained and ask for repeated injections. Again the drawback is the fleeting action of the drug which requires repeated injections. We are now experimenting with a synthetic drug with a curare-like action.

5. *Athetosis and Dystonia*. Besides the spastic paralysis combined with athetosis we have had the opportunity of studying the effect of curare upon adult athetotic, dystonic patients and upon post-encephalitic dystonic states. They relax temporarily for about 1 hour, after a curare injection. A patient had suffered from progressive, painful flexor spasms with athetosis and contracture of the right hand and foot for over 10 years. The etiologic factor was head trauma. Encephalographic Roentgen ray studies revealed atrophy of the basal ganglia, particularly on the left. All types of antispasmodic drugs and sedation had been ineffectual in relaxing the spasm or relieving athetosis. After a physiologic injection of curare, all evidence of contractural spasm and athetosis would dis-

appear and for several hours the patient would be free from pain. The effect, however, was fleeting and finally a premotor cortical resection was performed with permanent relief of the disorder.

6. *Hemiballismus*. (Syndrome of Corpus Luys.) We have recently had the opportunity of observing the effect of curare upon severe hemiballistic movements. A diabetic patient with evidence of generalized arteriosclerosis gradually developed severe chorea-like rolling, incoördinate movements of the left arm. These gradually spread, involving the left leg, trunk and face. After about 2 weeks of almost constant motion, the patient was admitted for hospital observation. The movements were not relieved by large doses of stramonium; under barbiturates the patient was able to obtain a few hours of sleep. After intravenous injection of aqueous curare, 10 mg. per 20 pounds of weight, complete relief from the movements was obtained for several hours. After intramuscular injection of concentrated curare, 20 mg. per cubic centimeters, the patient would fall asleep and obtain a full night's sleep. While these observations were being made, a pulmonary embolus suddenly developed and the patient died. Necropsy showed a thrombotic softening of the right globus pallidus and a small lesion of the right corpus Luys.

7. *Tetanus*. We have had opportunity to observe curare action in but 2 cases of tetanus. Both were moribund patients before curare therapy was attempted. In each instance, however, we have been able to produce relaxation of the continuous tetanic convulsion as long as curarization was continued. We believe it possible to perfect a continuous curarization technique that will prove to be extremely valuable in controlling convulsions of this disease. We believe that curare therapy offers more possibilities than sedative therapy in controlling tetanic convulsions.

Synthetic Curare. The collection and preparation of curare is a difficult task requiring expeditions by an expert explorer into South American jungles to procure adequate amounts of the potent non-toxic drug. We have, therefore, endeavored to find a drug with a curare-like action that would safely replace crude curare. Drugs having a curare-like action have been mentioned.

Quinine has been known for sometime to have a curariform action as shown by its relaxing effect upon myotonia congenita and dystonia musculorum deformans. It also aggravates the symptoms of myasthenia gravis. The commercially available quinine salts have a very weak curare-like action.

King⁶ has shown that in curare there are certain tertiary ammonium bases. It has been known that quaternary ammonium compounds formed by the addition of alkyl radical to the nitrogen atom of the quinoline ring have a curare-like action. King prepared a synthetic compound called quinine methochloride formed by the addition of the methyl group to the quinuclidine nucleus of

the quinine molecule. Harvey⁵ has shown that this drug has a strong curare-like action when administered either orally or parenterally.

Through the courtesy of E. R. Squibb and Sons research department, we were furnished with quinine methochloride for experimentation. An aqueous solution was prepared containing 20 mg. per cubic centimeter. Dr. A. R. McIntyre has compared in animals the reaction of quinine methochloride given intravenously with that of curare. He found with the former a curare-like action but not a pure curare effect as reported by Harvey. In the dog, the effect of quinine compared with that of curare is a rather marked drop in blood pressure with diminished respiration before complete cessation of nerve muscle contraction occurs; whereas the pure curare effect shows complete curarization of muscle or blocking of nerve impulses without any demonstrable drop in blood pressure or marked change in respiration. However, a definite transient paresis of muscles is produced, very similar to the action of curare, and in the patient is indistinguishable from curarization.

We have reported elsewhere² that the flaccid paresis following intravenous injection of quinine methochloride, 8 to 10 mg. per kilo, is sufficient to protect the patient from fractures in metrazol convulsions. In spastic paralysis we are able to obtain a complete curariform action after intravenous injection of 10 to 15 mg. per kilo of body weight. This curare effect wears off in from 10 to 15 minutes or can be completely counteracted by an intravenous injection of 1 to 2 cc. of prostigmin. A curarization effect can be produced by oral administration with about 8 times the intravenous dosage.

In 8 cases of spastic athetoid paralytic states and 1 case of Huntington's chorea, marked relaxation of rigidity and abolition of involuntary movements resulted from oral administration of 3 to 4 gm. (45 to 60 gr.) of quinine methochloride daily. The patients experienced marked subjective relief and definite objective improvement occurred while the patients were taking the drug. While these observations are based upon a very few cases, we believe that they are sufficient to conclude that this drug has possibilities for useful application to hyperkinetic and spastic neurologic disorders.

Summary. 1. Curare has successfully been applied to clinical neurologic therapy.

2. Its use as a preventive of traumatic complications in metrazol convulsive shock therapy has been proved.

3. Experiments with curare suggest an etiologic factor in botulism, ascending Landry's paralysis, and myasthenia gravis.

4. In spastic paralysis, athetoid and dystonic states, Parkinsonism, hereditary chorea, spasmodic torticollis, status epilepticus, tetanus and hemiballismus, curare produces a marked relaxation of rigidity and abolition of involuntary movements. Its action is

transient and fleeting, but continued experimentation should evolve a sustained action that will be therapeutically valuable.

5. A synthetic drug, quinine methochloride, has a curare-like action that is effective by mouth. This drug offers great possibilities, not only as a replacement drug for metrazol convulsive shock therapy, but in clinical neurology to relax hyperkinetic, spasmodic, and spastic states.

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BOOK REVIEWS AND NOTICES

RADIOLOGIC PHYSICS. By CHARLES WEYL, S. REID WARREN, JR., and DALLET B. O'NEILL, the Moore School X-Ray Laboratory, Moore School of Electrical Engineering, University of Pennsylvania. With a Foreword by EUGENE P. PENDERGRASS, M.D., Director of the Department of Radiology, University of Pennsylvania. Pp. 459; 166 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, \$5.50.

THIS book is the result of extensive teaching experience obtained from courses given to graduate students and Roentgen ray technicians since 1930. As a result, the exposition is clear and comprehensive. From the fundamentals of elementary electric and magnetic phenomena the reader is carried smoothly into analyses of electric circuits and electronics. Next electromedical apparatus is briefly covered with an excellent outline of high-voltage generators for Roentgen ray equipment. Part 2 of the book begins with the theory of radiation, including both the wave and the quantum theories, and goes into the production of Roentgen rays and their interaction with matter. The chapter on radioactivity and nuclear physics is a considerable aid in understanding the contemporary theories and applications of natural and artificial radioactivity. The remaining quarter of the body of the book is devoted to measurement, control and use of Roentgen rays and gamma rays in therapy, roentgenography and fluoroscopy. The appendix covers the elements of algebra, trigonometry and calculus, together with a four place table of logarithms, a table of exponentials and a table of natural trigonometric functions.

The subject material is well handled and there are many cross-references and excellent illustrations. There is an adequate bibliography at the end of each chapter. The book should be a great help to the student and Roentgen ray technician, and a good source book for the radiologist.

G. H.

AGE MORPHOLOGY OF PRIMARY TUBERCLES. By HENRY C. SWEANY, M.D., Medical Director of Research, Municipal Tuberculosis Sanitarium, Chicago, and Research Associate, Department of Physiology, University of Chicago. Pp. 265; 73 plates and 26 charts. Springfield, Ill.: Charles C Thomas, 1941. Price, \$5.00.

THIS book is of primary interest for pathologists but is of clinical importance as well. The author has attempted to set up criteria through which the age of primary tubercles can be determined by pathologic examination. He has reached these criteria by tracing the microscopic changes in a large series of primary tubercles of approximately known age, the latter being determined on the basis of known exposure to open tuberculosis in early life. The changes as represented by development and regression of successive anatomic phases in the tubercle have been weighted in a chart that the author has devised for determining the age of primary tubercles of unknown history.

Two chapters are of special concern for clinical medicine, *viz.*, one on the age of tubercles found in a group of nurses and hospital attendants, the other on the age criteria of primary tubercles as revealed by roentgenography. In this day when much attention is devoted to the question of transmission of tuberculous infection in hospitals, and to the respective rôles of exogenous and endogenous infection, the author's effort to date

the oldest tuberculous lesions in the body is timely. Unfortunately much less can be learned by roentgenography in life than by pathologic examination at necropsy. Only 20% of primary lesions are visible in antemortem films, and after calcification has become complete, a process consuming ordinarily 6 to 8 years, further changes that are conspicuous in microscopic sections cannot be detected by roentgenography.

The author's method of approach is logical and the conclusions impress the reader as sound. The book is well organized and the illustrations are numerous and excellent. The press work is commendable in every way.

E. L.

MACLEOD'S PHYSIOLOGY IN MODERN MEDICINE. Edited by PHILIP BARD, Professor of Physiology, Johns Hopkins University School of Medicine, with 9 Collaborators. Pp. 1256; 387 illustrations. Ninth edition. St. Louis: The C. V. Mosby Company, 1941. Price, \$10.00.

THREE years ago in its English edition, this standard textbook of physiology was completely revised, each section having been assigned to a specialist. This highly successful arrangement has been continued in the present edition. Revision is again extensive, the sections on circulation, respiration, metabolism and nutrition having been entirely rewritten, and a chapter added on the bladder. The quality of paper has been improved. In general, the new edition is a considerable improvement in a book already excellent.

M. McC.

GREEN'S MANUAL OF PATHOLOGY. Revised and Enlarged by H. W. C. VINES, M.A., M.D., Director of the Charing Cross Hospital Institute of Pathology. Pp. 1166; 701 illustrations. Sixteenth Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, \$8.50.

By greatly enlarging the book, revising some sections and rewriting others, a practically new textbook of pathology has been produced. The conventional division into the two sections of general and special pathology has been preserved. The inclusion of the avitaminoses in the chapter in general pathology on diseases of nutrition seems to the Reviewer most appropriate.

Despite a certain unevenness, the book as a whole is well suited to the needs of the beginner in pathology. Its value in stimulating the student to enlarge his knowledge by outside reading is greatly diminished by the omission of all references to the literature. It is to be hoped that the next edition will include a bibliography and that certain errors in the present one will be corrected, such as "Evehejm" for "Elvehjem" (p. 108), "vitamine" for "vitamin" (pp. 102-110) etc., and that a reference to the literature will make it clear whether "Meakin" or "Menkin" is meant (p. 133) in connection with fibrin formation and the localization of inflammation. The illustrations are very numerous, but some could be omitted without great loss.

E. W.

THE THERAPY OF THE NEUROSES AND PSYCHOSES. A Socio-Psycho-Biologic Analysis and Resynthesis. By SAMUEL HENRY KRAINES, M.D., Associate in Psychiatry, University of Illinois, College of Medicine; Assistant State Alienist, State of Illinois, etc. Pp. 512; 3 figures. Philadelphia: Lea & Febiger, 1941. Price, \$5.50.

THIS book, written by a psychiatrist for those not specializing in psychiatry, goes a long way in practical guidance. Most of the space is devoted to the analysis of neurotic symptoms and to the treatment of

neurotic patients. Neurotic symptoms are divided into those expressing tension and those used as symbols, a very helpful and clear way of presenting what are widely considered as meaningless phenomena. The reality of these symptoms is made more evident by the excellent passage showing the rôle of the autonomic nervous system in the production of tension symptoms. This discussion leads naturally into a simple, well documented, and specific treatment of psychosomatic disorders.

The suggestions given for therapy, while not of a very profound nature, are quite sound and practicable. There is an abundance of illustrative case material presented. The author has the happy faculty of presenting the best in psychobiology in a clear and simple way that will do much to take the mystery out of psychiatric practice.

The small amount of space given to the psychoses seems justified for the reason that by and large those not practising psychiatry will not have psychotic patients under their care. Manic-depressive psychoses are categorically called "physiologic illnesses." Convulsive therapy is highly recommended for the treatment of depressed patients, especially those in the involutional period. In regard to the insulin therapy of schizophrenia, the highly controversial statement is made that "the principle of this form of treatment is to produce some 15 to 25 insulin comas in the patient. This number is generally sufficient to cure most patients."

There are several other opinions about which the reader should be warned because they are stated as facts. "Cures are not more commonly obtained by psychoanalysis than by eclectic psychiatrists, and what cures are achieved through the psychoanalytic technique of treatment occur because its therapeutic value lies not in its elaborate superstructure . . ." "These same goals (of psychoanalysis) can be achieved far more simply and directly by the therapy as advanced elsewhere in this book . . ."

The author seems to feel that analysts would recommend psychoanalysis as superior form of therapy for all neuroses. This is, of course, not true and casts some doubt on the author's opinion in regard to Psychoanalysis in general.

Despite the above criticisms and an overly optimistic view prevailing throughout, this book is highly recommended to those for whom it is intended.

L. S.

AN INTRODUCTION TO DERMATOLOGY. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Emeritus Professor of Dermatology, University of Kansas School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., L.R.C.P. (EDIN.), Assistant Professor of Dermatology, University of Kansas School of Medicine. Pp. 904; 723 illustrations. Fourth Edition. St. Louis: The C. V. Mosby Company, 1941. Price, \$9.00.

THIS work continues to be one of the best short texts in dermatology available to the student and general medical man. The need for 4 editions in 9 years is, in itself, a tribute to its excellence and popularity. The present revision is considerably improved by the inclusion of a short and carefully compiled bibliography of leading articles in the readily available journals and by the addition of numerous carefully selected illustrations.

Although the section on syphilis covers many of the general medical and treatment aspects of the disease, it should not be regarded as adequate for the present-day needs of the student or general practitioner unless supplemented by considerable collateral reading.

The management of the common skin diseases is adequately covered and the majority of the rarer dermatoses are classified and briefly described.

N. I. JR.

RADIOLOGY PHYSICS. An introductory Course for Medical or Premedical Students and for all Radiologists. By JOHN KELLOCK ROBERTSON, F.R.S.C., Professor of Physics, Queen's University, Kingston, Canada. Pp. 270; 188 illustrations. New York: D. Van Nostrand Company, Inc., 1941. Price, \$3.50.

THE author assumes as prerequisite for the use of his book a knowledge of many of the elementary aspects of mechanics, radiation, and electricity and magnetism. He uses it as a text for a course given during the last year of a 2-year course in physics for pre-medical students. Although his treatment of the subject of electricity is elementary, it is not fundamental, and therefore cannot initially help a reader who wants to review the fundamental bases of electricity and magnetism.

The material which is presented is in general accurate and clear and the sections on the Conductivity of Air, Chemical Analysis by Positive Rays, The Meaning of Critical Absorption Wave-length, Causes of Grid Shadows, Absolute Intensity and Law of Inverse Squares and particularly the sections on the Cyclotron and on Radioactivity are extremely well written and well illustrated.

This book will be useful to medical students, radiologists and possibly some radiologic technicians as well. E. P.

HUTCHISON'S FOOD AND THE PRINCIPLES OF DIETETICS. Revised by V. H. MOTTRAM, M. A. (CANT.), Professor of Physiology at King's College of Household and Social Science, University of London, and GEORGE GRAHAM, M. D. (CANT.), F.R.C.P. (LOND.), Physician to St. Bartholomew's Hospital. Pp. 648; 27 illustrations. Ninth Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, \$6.75.

A book which has gone through 8 editions needs little comment. For those who are not familiar with it, a short outline may not be amiss. After some general observations on dietetics, the authors describe the functions of the foods in the normal diet, in providing energy and body building, with special chapters on the inorganic elements and the vitamins. The classes of foods are then taken up in greater detail with their composition and their place in the total dietary explained. Several chapters are devoted to the principles of feeding in infancy and childhood, and to the diet in the treatment of disease. These are so clearly presented that the fact that the details are based on English menus, tastes and meal hours, detracts only slightly from its value. Simple food tables make it easy to adjust the diet to any desired amount and distribution of the various foods.

The text is clear and readable and the index is sufficiently detailed so that no difficulty is found in locating any desired item. This book deserves the careful consideration of anyone desiring a book on dietetics. R. R.

ANUS, RECTUM, SIGMOID COLON. Diagnosis and Treatment. By HARRY ELLICOTT BACON, B.S., M.D., F.A.C.S., F.A.P.S., Clinical Professor of Proctology, Temple University School of Medicine; Associate Professor of Proctology, Graduate School of Medicine, University of Pennsylvania, etc. Introduction by W. WAYNE BARCOCK, A.M., M.D., LL.D., F.A.C.S., Professor of Surgery, Temple University School of Medicine. Foreword by J. P. LOCKHART-MUMMERY, M.A., M.B., B.C. (CANTAB.), F.R.C.S. (ENG.), Emeritus Surgeon, St. Mark's Hospital, London, England. Pp. 857; 507 text illustrations (mostly original) by WILLIAM BROWN MCNETT; 1 colored frontispiece. Second Edition. Philadelphia: J. B. Lippincott Company, 1941. Price, \$8.50.

THE second edition of this work is very similar to the first. It is an excellent and painstaking review of the literature and description of the

various diseases of the anus, rectum and sigmoid colon. The author has kept the book abreast of the times by adding the newer methods and drugs as they are applied to diseases of the lower bowel. The illustrations by McNett are outstanding and probably account for much of the popularity of this work. This book remains as a very excellent reference work for surgeons and practitioners interested in a monograph concerning diseases of the lower bowel.

L. F.

MODERN DRUG ENCYCLOPEDIA AND THERAPEUTIC GUIDE Presenting descriptions of 11,114 modern, non-pharmacoepal, ethical medicinal preparations in 15,629 forms, comprising: 3,421 drugs and chemicals, 663 biologicals, 691 endocrines, 2,270 ampoule medicaments, 3,190 individual and group allergens and 879 miscellaneous products. For the Use of Physicians, Dentists, Pharmacists, and Medical Students. By JACOB GUTMAN, M.D., PHAR.D., F.A.C.P., Director, Brooklyn Diagnostic Institute; Consulting Physician, Manhattan General Hospital, New York, the Riverdale, Shore Road, Williamsburg Maternity, and Borough Park General Hospitals of Brooklyn. Pp. 1644. Second Edition. New York: New Modern Drugs, 1941. Price, \$7.00.

As outlined in the Preface to the first edition of this book in 1934, its purpose is to provide a concise yet adequate and authoritative source of information for the physician about the many products of pharmaceutical manufacturers that do not find their way into New and Non-official Remedies. The Encyclopedia part (1303 pages, with distributors' index) contains an alphabetical list of such preparations, giving for each the name of the manufacturer, the composition, the claimed action and uses, the form, or forms, in which it is supplied, and the recommended dosage; the listings are offered without comment or change from the original sources. Preparations advertised and sold directly to the laity are not included. The Therapeutic Index (339 pages, with drug index) is an alphabetical catalogue of disease states under each of which are listed the preparations in the Encyclopedia that are recommended in that connection. As a reference book this provides in compact form a source of information about the composition of preparations which are more or less widely used and it will therefore be valuable to pharmacologists and toxicologists. The scientific therapist will also be enabled by it to arrive at his own decisions as to the probable value of the remedies listed herein compared with the simpler and much cheaper official preparations. The Therapeutic Guide seems to the Reviewer to be a complete anachronism; the book would be more dignified and no less valuable without it.

C. S.

ELECTROCARDIOGRAPHY IN PRACTICE. By ASHTON GRAYBIEL, M.D., Instructor in Medicine, Courses for Graduates, Harvard Medical School; Research Associate Fatigue Laboratory, Harvard University; Assistant in Medicine, Massachusetts General Hospital, and PAUL D. WHITE, M.D., Lecturer in Medicine, Harvard Medical School; Physician, Massachusetts General Hospital, in charge of the Cardiac Clinics and Laboratory. Pp. 319; 272 figures. Philadelphia, W. B. Saunders Company, 1941. Price, \$6.00.

In this atlas are illustrated the important abnormalities encountered in clinical electrocardiography. Brief case histories are supplied for correlation. Explanations are concise and clear. Of particular interest are the sections on the arrhythmias, and the considerable numbers of tracings showing borderline electrocardiographic abnormalities and their interpre-

tation. The inclusion of 129 "unknown" tracings toward the end of the book, with case histories and interpretations opposite, allows one to test his skill with that of the authors'. The Reviewer regrets that only one chest lead (CF-4) is used in the study of patients suspected of having coronary artery disease.

W. J.

BIOLOGICAL ASPECTS OF INFECTIOUS DISEASE. By F. M. BURNET, M.D., Assistant Director, Walter and Eliza Hall Institute, Melbourne. Pp. 310; 9 figures and 4 plates. Cambridge: The University Press; New York: The Macmillan Company, 1940. Price, \$3.75.

Books on infectious diseases have usually been written by medical men who have been interested chiefly in the effects of infection on man. This book is written by a biologist to whom both man and microorganisms are objects of equal interest. It treats infections as interactions between living species, *i. e.*, infectious agents (protozoa, bacteria and viruses) and their hosts. The author emphasizes that "we can deal with no restricted field in studying the nature of disease. The whole range of living beings comes into our province, for there is probably no species of organisms which has not at one time been either host to a parasite, or a parasite itself. Infectious disease is universal." The host-parasite relation is discussed from the ecologic point of view, as a struggle for existence between species which profoundly affect one another. Broadly viewed, the interactions lead to its development of an approximately balanced condition.

There are chapters on the processes within the body of the host which develop as the result of invasion by infectious agents, on the natural history of infectious disease, of its spread, on the general character of endemic disease and of epidemics, on some important infections which exemplify general principles, and finally on new diseases and the outlook for the future.

The book is very readable and should serve as a stimulating complement to more orthodox textbooks. The general reader interested in the relation of biology to human affairs will find here an excellent account of infectious disease as an important aspect of everyday life.

B. L.

THE COMPARATIVE PHYSIOLOGY OF RESPIRATORY MECHANISMS. (The William J. Cooper Foundation Lectures, 1939, Swarthmore College.) By AUGUST KROGH. Pp. 172; 84 illustrations. Philadelphia: University of Pennsylvania Press, 1941. Price, \$3.00.

THIS book represents a series of lectures given at Swarthmore College. It should be a valuable addition to the literature on comparative physiology, and serve a useful purpose not only for students but also for teachers and research workers.

The respiratory mechanisms of numerous species from small invertebrates to whales and man are discussed. The various examples are arranged "into a kind of physiological system, built up on analogy of function." A large number of zoölogic forms are considered and the species are carefully indexed. In addition 287 references to the original literature are given, so that the book will provide a rich mine of information on respiratory function to the zoölogist and comparative physiologist.

Many of the chapters present relatively simple facts which should be understandable even to a beginner in the subject, but this does not imply that the same chapters are not invaluable to the expert. The charm of the book lies in the originality, simplicity and clarity with which relatively simple facts are arranged and analyzed. The master hand of one of the outstanding living biologists is throughout in evidence.

H. B.

MASOCHISM IN MODERN MAN. By THEODOR REIK. Translated by MARGARET H. BEIGEL and GETRUD M. KURTH. Pp. 439. New York: Farrar & Rinehart, Inc., 1941. Price, \$4.00.

MASOCHISM is the desiring of discomfort and pain, and Freud has regarded it as our most common and important perversion. After having pondered the subject for 15 years, the author believes he has solved many of its intricacies. Debt is acknowledged to Freud for his insight into the nature of masochism but it is said he failed to arrive at its full understanding—pointed the way but did not go. Reik's thesis is discussed in eight parts: Problem, Phenomena, Dynamics, Origin, Sexes, Ego-Gains, Social Forms and Cultural Aspects. It is maintained that sexual masochism embraces the paradoxical pairing of discomfort and pain with sexual pleasure. In social masochism, the martyr attitude of modern man is seen to have developed. Fear of annihilation of the personality and the hope of immortality has led to the national masochism of today. The author's theories are difficult to follow. Philosopher Havelock Ellis wrote most lucidly on masochism; failure to consider these discussions, particularly his case of "Florrie," is more harmful to the author than to the philosopher.

N. Y.

DEBATABLE TUMOURS IN HUMAN AND ANIMAL PATHOLOGY. (Cancer Research Memoirs, No. 1.) By W. F. HARVEY, E. K. DAWSON, and J. R. M. INNES. From the Research Laboratory of the Royal College of Physicians, Edinburgh, the Cancer Control Organisation of Edinburgh and South-East Scotland, and the Institute of Animal Pathology, University of Cambridge. Pp. 124; 40 plates. Edinburgh: Oliver and Boyd, Ltd., 1940, for the Cancer Control Organisation of Edinburgh and South-East Scotland. Price, 10/6.

By "debatable tumours" the authors apparently do not mean lesions that are doubtfully neoplastic (though this idea also appears on occasions), but rather neoplasms the nature of which is debatable—as if this were not true to some degree for all neoplasms. The authors have selected for consideration 9 tumors which are "so debatable that a detailed argument on their nature seems justifiable." The seminoma they regard as a malignant epithelial tumor arising from the spermatoblast; the granulosa cell tumor as of primitive ovarian follicle origin; the "mixed tumor" of the parotid as an adenoma; the giant cell tumor of bone as a neoplastic growth intermediate between purely reactive tissue and a true blastoma. Among melanomas the authors include benign nevus cell tumors, and pigmented tumors of mesodermal origin; the malignant melanoma they regard as a melanocarcinoma. Endothelioma may be either benign or malignant, "vasoformative" or "membraneoformative"; meningioma arises from stem-cells of endothelial type. Lymphosarcoma arises from a primitive mesenchymal cell, which has "productive potentialities of endothelioblast, fibroblast and lymphoblast." The terms "reticulum-cell, lympho- and endothelial sarcoma" are used interchangeably. "Lymph epithelioma" is considered as covering two types of malignant growth: carcinoma and lymphosarcoma. The suffix "-blastoma" apparently is used to indicate malignancy.

Thus the reader may not infrequently find his tumor concepts at variance with the authors' views, who incidentally express regret for a dogmatism necessitated by limitations of space. He cannot fail to profit, however, from the clearly stated results of the obviously careful study of a large amount of tumor material. The numerous excellent photomicrographs and the bibliography of Directional Literature are also to be commended. The lack of an index is a striking defect.

E. K.

A TEXTBOOK OF CLINICAL NEUROLOGY. By J. M. NIELSEN, B.S., M.D., F.A.C.P., Associate Clinical Professor of Medicine (Neurology), University of Southern California; Senior Attending Physician (Neurology), Los Angeles County General Hospital; Attending Neurologist, Hospital of the Good Samaritan, Los Angeles. Pp. 672; 179 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, \$6.50.

This is a very practical book written in plain language. Students and physicians alike will here find the answers to their neurologic problems. The clinical picture of the various diseases is built up on the anatomy of the diseased parts of the nervous system, their function and pathology. Photographs and diagrams facilitate the comprehension. The methods of differential diagnosis and treatment are clearly stated and the use of recent drugs such as the sulfonamides and the vitamins are discussed. The book is written, as the author explains, in a somewhat dogmatic style since the enormous material had to be limited in some way. It is unavoidable under these conditions that the author's opinion will not be always shared by others. This danger is lessened by bibliographies accompanying each chapter, giving the reader an opportunity to follow up details if he is interested in controversial questions. The presentation reflects throughout the experience of the author as neurologist and as teacher. The book is recommended as a textbook for students and as a reference book for physicians.

F. L.

SPERMATOOZOA AND STERILITY. A Clinical Manual. By ABNER I. WEISMAN, M.D., Adjunct Gynecologist, Jewish Memorial Hospital; Clinical Assistant Visiting Gynecologist and Obstetrician, Metropolitan Hospital, New York. With a Foreword by ROBERT L. DICKINSON, M.D. Pp. 314; 77 illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, \$5.50.

The present volume would be a useful addition to the library of the general practitioner, urologist and gynecologist. As its name implies, it is essentially a hand book of practice. Its contents deal primarily with the practical details of studying the seminal fluid, and the proper interpretation of the findings. An interesting part of the work concerns the question of artificial insemination and its medico-legal aspects. Other chapters deal with the author's original contribution to the subject. The material is well arranged, and the illustrations are excellent. The volume contains much that is of general interest, apart from its practical aspects. An excellent bibliography of some 764 titles is appended.

D. M.

ROENTGEN INTERPRETATION. By GEORGE W. HOLMES, M.D., Roentgenologist to the Massachusetts General Hospital and Clinical Professor of Roentgenology, Harvard Medical School, and HOWARD E. RUGGLES, M.D., Late Roentgenologist to the University of California Hospital and Clinical Professor of Roentgenology, University of California Medical School. Pp. 364; 246 illustrations. Sixth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$5.00.

In 1919, in the preface to the First Edition, the authors remarked that it was their hope that "this book will prove of particular aid to those in search of a working knowledge in roentgen interpretation." The fact that the work is now in its Sixth Edition bears ample testimony to the success of their purpose.

The outstanding characteristics of this work continues to be its clearness and brevity. As in the past, the authors have not attempted to present their material in an exhaustive fashion. Because of this, the manual is admirably suited for use by students and physicians other than radiologists.

The general characteristics of the book are unchanged, the illustrations are essentially the same. The authors have added to the chapter on Diseases of Bone, a brief résumé of sarcoidosis, Ollier's disease and the bone changes seen in erythroblastic anemia. A discussion on the recent advances in the diagnosis of intramedullary spinal cord tumors is also new. The chapter on Diseases of the Chest now includes references to mediastinal herniation, pericardial tumors, and tuberculous ulcerations of the bronchi associated with atelectasis. The diagnosis of lymphoblastoma of the lung are also included in this chapter. The chapter on the small intestines has been augmented by a discussion of small intestinal tumors.

Whereas the volume is well illustrated, it is hoped that the next edition will appear with positive illustrations changed to negative illustrations.

P. H.

THE MASK OF SANITY. An Attempt to Reinterpret the So-called Psychopathic Personality. By HERVEY CLECKLEY, B.S., B.A. (OXON.), M.D., Professor of Neuropsychiatry, University of Georgia School of Medicine, Augusta. Pp. 298. St. Louis: The C. V. Mosby Company, 1941. Price, \$3.00.

THE individual commonly known as a "psychopath" is regarded by the author as psychotic and irresponsible, thus rendering him immune to punishment. But such subjects know the nature and quality of their acts of misbehavior, also that they are punishable; and knowing their weaknesses, it becomes their duty to fortify themselves by self-restraint; failing to do so, they render themselves liable to punishment. We already have a group whom psychiatrists regard as showing partial or limited responsibility, a condition which some courts recognize. While not offering a classification of his own, Cleckley comments favorably upon those of Noyes (who regards the condition as an expression of unconscious conflict) and of Kahn, who has made valuable contributions. There are 12 case reports revealing the disorder, and 6 others wherein it is partly manifested. Without clearly defining the condition, considerable space is devoted to its distinction from other personality disorders, some being the orthodox psychotic, the psychoneurotic, the mental defective, the ordinary criminal, sexual deviates, the erratic man of genius, the neurotic drinker, the malingerer, and fictional characters showing personality anomalies. While not solving this intricate problem, the author has given us an interesting treatise, including much pertinent matter by others. Being a writer of fiction also, he has employed a style less rigid than that of the scientist.

N. Y.

MANUAL OF CLINICAL CHEMISTRY. By MIRIAM REINER, M.Sc., Assistant Chemist to The Mount Sinai Hospital, New York. Introduction by HARRY SOBOTKA, Ph.D., Chemist to The Mount Sinai Hospital, New York. Pp. 296; 18 illustrations and 17 tables. New York: Interscience Publishers, Inc., 1941. Price, \$3.00.

THIS is a valuable little book of handy size. It is thoroughly practical, having had its origin in the need of laboratory interns for a source of precise technical detail "in the middle of the night." It is surprisingly complete and should appeal as a source of reference particularly to those lone and many-sided laboratory technicians in smaller hospitals who are not called on every day to do determinations which are routine matters in larger institutions. The contents are chiefly quantitative methods of blood and urine analysis, but there are also included the usual qualitative chemical

tests on urine, feces, spinal fluid and gastric juice. Unexpected welcome inclusions are some toxicologic tests, methods for sex hormones, Quick's prothrombin method, and technique of extracting allergens for subsequent skin-testing from naturally occurring source materials; also some photoelectric colorimeter methods, methods for vitamins, technique for biliary and urinary calculus analysis, and even the Takata-Ara test. For each method there is a key reference to the literature (all of which add up to a sizeable bibliography), and there is an author index. D. B.

MECHANISMS OF BIOLOGICAL OXIDATIONS. By DAVID E. GREEN, Senior Beit Memorial Research Fellow, Institute of Biochemistry, University of Cambridge. (Cambridge Biological Studies, General Editor, C. H. Waddington.) Pp. 181; 22 figures. Cambridge: The University Press, 1940; New York: The Macmillan Company, 1941. Price, \$2.75.

CELLULAR oxidation is one of the basic phenomena of life. This book treats of the mechanisms of biological oxidations and discusses the enzyme systems in the cells upon which oxidation depends. Although most of our knowledge of such mechanisms is derived from experiments on but a few types of cells, a great store of information is now available. This monograph gives an excellent summary of biologic oxidation by a well-known investigator who has made significant contributions in this important field. B. L.

A DIABETIC MANUAL FOR THE MUTUAL USE OF DOCTOR AND PATIENT. By ELLIOTT P. JOSLIN, M.D., Sc.D., Clinical Professor of Medicine Emeritus, Harvard Medical School; Medical Director George F. Baker Clinic at the New England Deaconess Hospital; Consulting Physician, Boston City Hospital. Pp. 238; 53 illustrations. Seventh Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$2.00.

THE seventh edition of this very useful book maintains the standard set by its predecessors. In addition to the information which the book contains, it continues to be written with that hope for the future of the well trained diabetic which the author knows so well how to present. Two chapters of questions and answers combine with easily understood diet instructions to make this a book without which no diabetic can afford to be. The physician also will find much here to interest him, especially as regards the newer advances in diabetes. R. R.

SCIENCE AND SEIZURES. New Light on Epilepsy and Migraine. By WILLIAM G. LENNOX, M.D., Sc.D., Hon. Assistant Professor of Neurology, Harvard University Medical School; Visiting Neurologist, Boston City Hospital; etc. Pp. 258; 10 figures. New York: Harper & Brothers, 1941. Price, \$2.00.

CONSIDERATION of the nature and treatment of convulsive and headache seizures is the purpose of this book. In 1929, Hans Berger, German psychiatrist, demonstrated that when the electric currents of the brain were enormously amplified, they could be detected in the scalp and recorded on moving paper. The pattern of the resulting electroencephalogram (shortened to "E.E.G.") is quite characteristic of each individual. During a convulsion, the waves are increased in size and frequency. Grand mal shows a rapid dysrhythmia, in a psychomotor attack it is slow, and in petit mal the rhythm is alternating. A minor dysrhythmia is also present

when attacks are absent. Severe seizures may be predicted in advance. Sedation used in epilepsy, causes a slowing of cortical rhythms. Tantrums and some mental disorders show definite dysrhythmias. At present the matter of expense is a serious one; the instrument is expensive and a skilled operator and interpreter is required. In treatment, the new drug, dilantin sodium, is frequently of value. One notes that Napoleon has been omitted from the long list of great epileptics; Byron and Peter the Great should have been also. In migraine, it is the vegetative nervous system that is chiefly affected; there are no known brain changes. Ergotamine tartrate is a new and useful remedy, though considerable nausea follows its injection. Lennox has illuminated one of the dark realms of medicine. N. Y.

MANUAL OF PHYSICAL DIAGNOSIS with Special Consideration of the Heart and Lungs. By MAURICE LEWISON, M.D., Professor of Physical Diagnosis, University of Illinois College of Medicine; Consulting Physician, Cook County Hospital, etc., and ELLIS B. FREILICH, M.D., Associate Professor of Medicine, University of Illinois College of Medicine; Professor of Medicine, Cook County Graduate School of Medicine, etc. In collaboration with GEORGE C. COE, M.D., Instructor of Medicine, University of Illinois College of Medicine; Associate Physician, Cook County Hospital; Clinical Assistant, Mount Sinai Hospital, Chicago. Pp. 317; 75 illustrations. Chicago: The Year Book Publishers, Inc., 1941. Price, \$3.00.

This manual is the outgrowth of the outline which the Senior author has used in teaching the principles of physical diagnosis to his students.

"Systemic examination" of everything above the clavicles is covered in 9 pages. Five pages are allotted to the physical examination of the upper and lower extremities and the joints. Neurological examination is confined to a description of reflexes in less than 3 pages. That portion of the book which deals with physical examination of the thorax and the abdomen is adequate.

The Reviewer suggests that, if this book reaches a second edition, sufficient space should be allotted to "systemic examination," examination of the extremities and joints and that a chapter be added on physical examination of the nervous system. The requisite space can be achieved by omitting Diseases of the Bronchi, Lungs and Pleura (23 pages) and Diseases of the Cardiovascular System including Chronic Valvular Heart Disease, Subacute Bacterial Endocarditis, Diseases of the Pericardium, Angina Pectoris and Coronary Occlusion, Aneurysm of the Thoracic Aorta and Congenital Heart Disease (15 pages). S. L.

MEDICINE AND HUMAN WELFARE (The Terry Lectures). By HENRY E. SIGERIST, M.D., D.Litt., William H. Welch Professor of History of Medicine in the Johns Hopkins University. Pp. 148; 20 illustrations. New Haven: Yale University Press, 1941. Price, \$2.50.

THIS, the 16th volume of the Terry Lectures on "Religion in the Light of Science and Philosophy," conforms well with the aims of the Terry Foundation to advance the human race by promoting the interpretation of scientific discoveries and their application to human welfare. These lectures bear on religion, broadly interpreted, in the same sense as do earlier ones in the series, such as Compton's "Freedom of Man," and Barcroft's "The Brain and Its Environment."

The present series explores one of Dr. Sigerist's leading beliefs—the need for a better application of the triumphs of medical science to a basically changed society that is still in a period of transition. The first section, on

disease, shows the changing attitude toward disease through the centuries and touches on historic pestilences as examples of social illnesses that profoundly affected society. The second section, on health, considers the ups and downs of hygiene in ancient, mediæval and modern times. Among the topics considered are: the Greek and Roman successes in attaining a sound mind in a sound body, Johann Peter Frank and the concept of governmental control of public health in the 18th century, Chadwick and the English public health movement in the 19th, the failure of the German national health program of a century ago, and the gradual growth, with the development of medicine and engineering sciences, of a public health movement reaching well beyond the fields of sanitation and communicable diseases. In the third section, a survey of the physician's activities through the ages leads up to his widened sphere in today's social structure, including his integral relations to the law, education, industry and so on. Recognizing that the "technology of medicine has outrun its sociology," Dr. Sigerist proposes the drastic remedy that the physician be removed from the competitive business of private practice and that ultimately medical care be made a free public service. Though he recognizes that the financing of health care by taxation or insurance must depend to some degree on circumstances, he obviously favors the Soviet system of health planning, training of personnel and the prevention and treatment of disease as entirely a function of the government.

In their judicious selection from a great wealth of material and their dignified, entertaining style, these lectures present in attractive form an aspect of modern medicine that is of the highest importance for all physicians to comprehend and consider, even if they may not agree with the conclusions drawn and inferred.

E. K.

PEDIATRIC BIBLIOGRAPHY. By A. GRAEME MITCHELL, Department of Pediatrics of the College of Medicine, University of Cincinnati, and The Children's Hospital Research Foundation, Cincinnati. (Monographs of the Society for Research in Child Development, Vol. VI, No. 1, Serial No. 27.) Pp. 119 (lithoprinted). Washington, D. C.: Society for Research in Child Development, National Research Council, 1941. Price, 75c.

A WORKING bibliography of Pediatric literature based on material gathered mostly by Dr. J. P. C. Griffith and his colleague, Dr. A. G. Mitchell for their textbook. It makes no pretense of being complete for the field of Pediatrics or for any one subject but will be useful as a springboard to any specific section or disease of childhood.

E. T., Jr.

NEW BOOKS.

Oral Pathology. A Histological, Roentgenological, and Clinical Study of the Diseases of the Teeth, Jaws, and Mouth. By KURT H. THOMA, D.M.D., Professor of Oral Surgery, and CHARLES A. BRACKETT, Professor of Oral Pathology, Harvard University. Pp. 1306; 1370 illustrations, including 137 in color. St. Louis: The C. V. Mosby Company, 1941. Price, \$15.00.

Das Vitamin K und Seine Klinische Bedeutung. By DR. FRITZ KOLLER, Privatdozent für Innere Medizin an der Universität, Zürich. Mit Einem Geleitwort von Prof. Dr. W. LÖFFLER, Zürich. Pp. 151; 15 illustrations. Leipzig: Georg Thieme, 1941.

Medical Manual of Chemical Warfare. (First American Edition; Reprinted by Permission of The Controller of His Britannic Majesty's Stationery Office.) Pp. 119; 1 figure and 10 plates. Brooklyn: Chemical Publishing Company, Inc., 1941. Price, \$2.50.

The Medical Clinics of North America, Vol. 25, No. 3 (New York Number, May, 1941). Pp. 265; 8 illustrations. Philadelphia: W. B. Saunders Company, 1941.

Hernia. In Three Sections. Historical Evolution of Hernial Surgery; Technical; Medico-legal Aspects. By ALFRED H. IASON, B.A., M.D., Consulting Surgeon, Long Beach Hospital; Director of Surgery, Brooklyn Hospital for the Aged; Surgeon, Manhattan General and Madison-Park Hospitals, etc. Pp. 1325; 355 illustrations by ALFRED FEINBERG, Instructor of Medical Illustrations, Department of Pathology, College of Physicians and Surgeons, New York City. Philadelphia: The Blakiston Company, 1941. Price, \$15.00.

Biology of the Laboratory Mouse. By The Staff of The Roscoe B. Jackson Memorial Laboratory. CLARENCE C. LITTLE, Director, GEORGE D. SNELL, Editor, J. J. BITTNER, A. M. CLOUDMAN, E. FEKETE, W. E. HESTON, W. L. RUSSELL, G. W. WOOLLEY. With a Chapter on Infectious Diseases of Mice by J. H. Dingle, Harvard Medical School. Pp. 497; 172 illustrations. Philadelphia: The Blakiston Company, 1941. Price, \$7.00.

The British Encyclopedia of Medical Practice Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. *Complete Index.* Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., Professor of Medicine, University of London, etc., G. GREY TURNER, D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., Professor of Surgery, University of London, etc., JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., Professor of Obstetrics and Gynæcology, University of London, etc., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., Late Physician, Hospital for Tropical Diseases, London, and F. M. R. WALSH, O.B.E., M.D., Sc.D., F.R.C.P., Physician in Charge of the Neurological Department, University College Hospital. Pp. 486. London: Butterworth & Co. (Publishers), Ltd., 1941. Price, \$10.00.

Conditioned Reflexes and Psychiatry. (Volumes 1 and 2 of Lectures on Conditioned Reflexes. Twenty-five Years of Objective Study of the Higher Nervous Activity [Behavior] of Animals.) By IVAN PETROVITCH PAVLOV, Late Director, Physiological Laboratories, Institute of Experimental Medicine and Academy of Sciences, Leningrad; Late Professor of Physiology, Military Medical Academy, Leningrad, etc. Translated and Edited by W. HORSLEY GANTT, M.D., B.Sc., Medical Director, Leningrad Unit American Relief Administration, 1922-23; Co-worker in Pavlov's Laboratory, Institute of Experimental Medicine, 1925-29; Associate in Psychiatry and Director, Pavlovian Laboratory, Johns Hopkins University. (Vol. 1 with the Collaboration of G. VOLBORTH, M.D., Former Assistant to Professor Pavlov at the Military Medical Academy; Professor of Physiology, University of Kharkov, and an Introduction by WALTER B. CANNON, M.D., S.D., George Higginson Professor of Physiology, Harvard University.) Pp.: Vol. 1, 414 and 9 illustrations; Vol. 2, 199 and 7 illustrations. New York: International Publishers, 1931. Price, Vol. 1, \$3.50; Vol. 2, \$4.00.

Essentials of Endocrinology. By ARTHUR GROLLMAN, Ph.D., M.D., Associate Professor of Pharmacology and Experimental Therapeutics in the Medical School of The Johns Hopkins University. Pp. 480; 74 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, \$6.00.

The New International Clinics, Volume 2, New Series 4, June 1941. Edited by GEORGE MORRIS PIERSON, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, with 17 Collaborators. Pp. 299; illustrated; 1 colored plate. Philadelphia: J. B. Lippincott Company, 1941.

A wide range of subjects is covered in this number. Several "clinics" are presented from Yale and from three Lexington institutions. The "Review of Recent Progress" is on Chronic Gastritis, though the first article, on "The Functions of the Adrenal Glands" is also a digest (13 pages).

Proceedings of Meetings of the New York Pathological Society held Nov. 30 and Dec. 28, 1939, and Jan. 25, Feb. 29, March 28, April 25, and May 23, 1940. (Reprinted from the Archives of Pathology, March, June, August, September, and October, respectively, 1940.) Pp. 39.

Prostata-Krebs wie Paraprostata-Hypertrophie sind Folgen hormonaler Störungen, die wir je früher je besser beeinflussen können. 13 Jahre hormonale Krebs-Prophylaxe wie auch hormonale Behandlung der Paraprostata-Hypertrophie bei mehr als 1000 älteren Menschen. By DR. MED. PAUL NIEHANS, Chirurg und Urologe F. M. H. der Klinik von Clarens und der Spitäler von Vevey und Montreux (Schweiz). Pp. 48. Bern: Hans Huber, 1940.

NEW EDITIONS.

The Principles and Practice of Ophthalmic Surgery. By EDMUND B. SPAETH, M.D., Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania, Philadelphia; Attending Surgeon, Wills Hospital, etc. Pp. 886; 451 engravings containing 1149 figures and 6 colored plates. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$10.00.

Dietetics for the Clinician. By Late MILTON ARLANDEN BRIDGES, B.S., M.D., F.A.C.P., Director of Medicine, Detention, Rikers Island and West Side Hospitals, New York; Consulting Physician, Seaview Hospital, Staten Island, N. Y.; and Department of Education, New York University, New York, etc. Pp. 960. Fourth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$10.00.

Clinical Aspects of the Electrocardiogram including the Cardiac Arrhythmias. By HAROLD E. B. PARDEE, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital; Consulting Cardiologist, Woman's and Methodist Hospitals, etc. Pp. 434; 219 illustrations on 102 figures. Fourth Edition, revised. New York: Paul B. Hoeber, Inc., 1941. Price, \$5.75.

Fractures and Other Bone and Joint Injuries. By R. WATSON-JONES, B.Sc., M.Ch. ORTH., F.R.C.S., Civilian Consultant in Orthopaedic Surgery of the Royal Air Force, etc. Pp. 724; 1034 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, \$13.50.

Synopsis of Diseases of the Heart and Arteries. By GEORGE R. HERRMANN, M.S., M.D., Ph.D., F.A.C.P., Professor of Medicine, University of Texas; Director of the Cardiovascular Service, John Sealy Hospital; Consultant in Vascular Diseases, U. S. Marine Hospital. Pp. 468; 91 illustrations. Second Edition. St. Louis: The C. V. Mosby Company, 1941. Price, \$5.00.

Foundations of Neuropsychiatry. By STANLEY COBB, A.B., M.D., Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist in Chief, Massachusetts General Hospital. Pp. 231. Second Revised and Enlarged Edition of the Work formerly known as A Preface to Nervous Disease. Baltimore: The Williams & Wilkins Company, 1941. Price, \$2.50.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER, M.D.,
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CHRONIC CONSTRICTIVE PERICARDITIS.

THERE has been much confusion in the use of the term adhesive pericarditis. Adhesions of the visceral and parietal pericardium may or may not interfere with cardiac function and therefore may or may not produce symptoms. In one autopsy series^{46a} of 144 patients with partial and complete adhesive pericarditis only 57 (39.5%) presented complaints which made the heart the major issue in the clinical picture, and 47 of these had associated heart disease, leaving 10 with an adherent pericardium alone. Of the 47 with associated cardiac disease, 25 had rheumatic heart disease with aortic or mitral lesions or both. Adhesions vary from a few thin strands connecting the visceral and parietal pericardium to complete obliteration of the cavity, as well as external adhesions to the pleural and mediastinal structures—so-called mediastino-pericarditis.

Adhesive pericarditis may be classified into two varieties, that with constriction of the heart and that without. The non-constrictive variety may show partial or complete obliteration of the pericardial cavity as well as mediastinal adhesions. Symptoms arise in such patients upon two bases. The first is associated heart disease, which occurs frequently as stated above. In such patients the cardiac symptoms and signs are almost invariably produced by the associated disease. This is true, for example, in rheumatic heart disease. Associated adhesive pericarditis, although produced by the rheumatic fever as the result of more acute forms, consists of light non-constricting adhesions which for the most part give few or no symptoms. The second is tugging and pulling on mediastinal structures by adhesions. This, if it produces marked angulation or torsion of the heart, could produce hypertrophy of the heart, obstruction to inflow and similar changes.

There has been much dispute in the literature concerning the effect of non-constricting adhesions alone, without associated heart disease, upon the heart size and the production of cardiac hypertrophy.^{24,26,32,37,39} In some reports, hypertrophy is recorded; in others none was found

at all. Armstrong¹ has adequately reviewed this subject. With adherent pericardium as the only cardiac disease one autopsy series^{46a} showed a widely varying heart weight with marked increases in certain instances. No instances of hypertrophy have been reported in several similar series. Hosler and Williams²⁶ believe that adhesions *per se* do not cause circulatory embarrassment unless extensive enough to cause cardiac compression. They found no instances of hypertrophy in the presence of extensive pericardial adhesions unless associated disease was present. In 76 patients the only instances of hypertrophy with pericardial adhesions occurred in 54 patients with assignable cause. In Smith and Willis^{46a} series coronary sclerosis and rheumatic heart disease were present in slightly over 21% each, and hypertension in 17.4%. Beck^{3a} does not believe that adhesions play a rôle in heart failure, cardiac dilatation or hypertrophy. Both his clinical and experimental evidence supported the view that non-constricting adhesions were silent and incidental unless they produced twisting or angulation. Such adhesions form the picture which is often seen at autopsy when not at all suspected during life. Further evidence that complete adhesions between the two pericardial surfaces of and by themselves do not necessarily interfere with function to an important degree has been obtained by the deliberate production of adhesions by the introduction into the pericardial cavity of such materials as magnesium silicate or talc⁴⁸ and carborundum sand²³ to establish collateral circulation for coronary disease. This has been done in experimental animals, and, with talc, in humans without the development of cardiac embarrassment. The adhesive pericarditis of rheumatic heart disease falls into this class. Rheumatic fever, although it produces acute fibrinous pericarditis and pericarditis with effusion, eventuates in adhesions which are not thick, dense and constricting. Such changes may involve surrounding tissues at times drawing upon the mediastinal structures and chest wall.

The adherent pericardium, when thickened and constricting produces at times a typical and dramatic clinical picture. Chronic compression results from a variety of anatomic lesions,^{3a} for example, pericardial effusion, scar, and neoplasm, or a combination of these. A thickened contracting pericardium which may or may not be adherent is the usual cause. Beck has seen the picture produced by intermittent hemorrhage from sarcoma involving the pericardium, and some⁴⁰ believe that a fibrous pericardium may interfere with cardiac function in patients with marked hypertrophy. The remaining remarks will be devoted to chronic constrictive pericarditis resulting from a thickened fibrous pericardium.

An historical review of chronic constrictive pericarditis has been given by White^{51a} and will not be repeated here. The term is applied, as stated above, to pericardial disease, producing a thickened unyielding coat which interferes with diastolic filling of the heart. Pick⁴² gave the name pseudocirrhosis of the liver to the disease, which in his patients included not only mediastinopericarditis but polyserositis and chronic inflammation of the pleura and peritoneum. Many terms have been applied to the disease. Besides Pick's disease, chronic constrictive pericarditis and pericardial pseudocirrhosis of the liver, these include adhesive pericarditis, chronic obliterative pericarditis, concretio peri-

cardii, symphysis cardiaca, mediastino-pericarditis, Concato's disease and polyserositis. The use and abuse of some of these terms has already been given. More will appear as the discussion progresses.

Etiology. In many instances the cause of chronic constrictive pericarditis rests upon unknown grounds. From what has already been said, rheumatic fever is not under suspicion. None of White's 28 patients had rheumatism and that is the experience of others.¹ There are, however, a number of reported patients⁴⁹ in whom a history of rheumatism has been obtained. However, it is difficult to evaluate the term in the light of rheumatic fever. In several instances where such a history has been obtained the autopsy findings in the heart did not bear out the presence of rheumatic valvulitis.

Many possible etiologic agents have been considered. These include tuberculosis, syphilis, pericardial trauma,¹⁸ and pyogenic involvement of the pericardium directly from the lung or by metastasis from foci of infection, for example, by streptococcus,³⁶ pneumococcus,¹² and staphylococcus.^{8,30} The development of chronic constrictive pericarditis from acute inflammatory pericarditis produced by such infections has not been well understood, because of the long periods between the clinical pictures at times. The number of patients followed through in this way is increasing. In several reported instances also, pus pocketed in the constricting pericardium has shown the offending organism.^{8,30}

Tuberculosis is definitely known to produce the picture^{1,22} even though by the time the chronic stage is reached there is often doubt in the diagnosis. In Burwell and Blalock's group of 19 patients,^{5,7} 16 were considered to have tuberculous pericarditis, and in 11, tubercles were demonstrated microscopically. This is the only report with an appreciable incidence of tuberculosis. Others have obtained strikingly different figures.^{1,3a,31,51a,b} Beck says that about 10% are tuberculous.

Purulent pericarditis is known to eventuate in chronic constrictive pericarditis. In the past operative intervention for purulent pericarditis has been condemned because of the frequent complication of obliterative pericarditis.⁴⁵ However, Shipley and Winslow's reports^{45,52} include 39 cases to support the opposite view that fatal obliterative pericarditis is not the inevitable outcome. After 1 to 32 years, 35 patients were alive, well, and working as usual. Two (5.13%) had pericardial symptoms.

Purulent pericarditis⁴⁵ in most cases is attributed to metastases from foci of infection, such as osteomyelitis and other suppurative processes, especially pneumococcal, staphylococcal and streptococcal. Occasionally purulent pericarditis results from bullet and stab wounds. Purulent pericarditis tends to cause local adhesions anteriorly because the heart is said often to be against the anterior wall of the sac. In Shipley and Winslow's case the exudate had pushed the heart forward into juxtaposition to the pericardium, producing adhesions.

Many instances of chronic constrictive pericarditis cannot be traced back to acute pericarditis of known etiology. In only half of Smith and Willius's series of 144 patients with pericardial adhesions were causes found for the changes seen.^{46a} In the 28 patients of White's series^{51b} the etiologic agent was unknown in most instances.

Age incidence varies through a wide range. In White's series

again onset of the disease was noted from $5\frac{1}{2}$ to 51 years. Only 5 patients were beyond the age of 40. Others have seen older patients but in general it is primarily a disease of children and young adults. Males are more often affected than females in a ratio of about 3 to 1 down to 2 to 1. It is interesting to note that the sex ratio, males to females, in purulent pericarditis was $2\frac{1}{2}$ to 1 in 73 instances,⁴⁵ a strikingly similar figure which again tends to associate purulent with constrictive pericarditis.

Pathology. No attempt will be made to cover thoroughly the pathologic aspects. The acute processes already mentioned above may progress to a chronic stage with thickening, fibrosis, calcification and constriction. The heart cannot relax sufficiently in diastole. As Sprague⁴⁷ states, the heart chambers are fundamentally normal but blood is prevented from entering them because of interference with the capacity of the chambers to dilate and receive blood because of the inelastic armor of the thickened pericardium. Complete adhesions of the visceral and parietal layers are not necessary but are the rule. One or the other layer or both may be chiefly responsible. This fibrosis may be localized or diffuse. The type of fibrous tissue differs from that seen in non-constrictive adhesive pericarditis.¹ It is thicker and denser with considerable hyalinization. The anterior surface is usually the area most involved, and pocketing of fluid which at times contains the causative organism occurs. Adhesions to the chest wall may be a part of the pathologic picture but are not a part of the clinical picture.

Calcification occurs in a variable number of cases, according to White,^{51b} about one-third. Definite descriptions of calcified pericardium go back 200 years.¹² In 1924 Turner⁴⁹ in thoroughly reviewing the literature found some 89 cases and added 3 of his own. The diagnosis has been a rarity in the past but with frequent use of roentgenograms is becoming more and more common. A large number of known cases are not reported also. It is more often absent than present, in constrictive pericarditis and may occur in adhesive pericarditis without constriction.¹ It was present in 10.4% of 144 cases^{46a,b} having adhesions of all degrees. In Jones' collected group of 56 patients with calcified pericardium,²⁸ he found 5 with a history of acute rheumatism, 5 with vague rheumatic pains and 11 where absence of a history of rheumatism was absolutely stated.

The cause of calcification is obscure. It is said to occur in dead or dying tissues and in inspissated exudates. Wells⁵⁰ made these statements in this journal in 1902. To him it seemed that calcification of adhesions was not common, and in his group of 4 patients calcification of inspissated exudates seemed more likely in such infections as the pneumococcus produces rather than in tuberculosis. Others^{46a} also believe that calcification is the end-result of inflammatory disease, more particularly that which is non-tuberculous. Hemorrhage into the pericardium is given as a cause of calcification.

The effects of adhesions upon heart size have already been discussed. The compressed heart of constrictive pericarditis is a "quiet" organ.^{2a} It cannot dilate and receives too little blood so that it puts out too little blood. Beck believes that such a heart can and does undergo atrophy of disuse with reduced work.

The relationship of polysclerosis, so-called Concato's disease, to con-

strictive pericarditis is not clear. Constrictive pericarditis may occur with or without polyserositis and polyserositis with or without constrictive pericarditis. The two frequently occur in the same patient. Polyserositis is occasionally found in young individuals due to tuberculosis or associated with pneumonia or unknown cause.^{51b} The perihepatitis and perisplenitis, so-called frosted or iced liver and spleen, are regarded as part of a chronic peritonitis. The process, presumably infection, has associated with it exudation in the serous cavities, pleura, pericardium and peritoneum.

The work of Beck⁴ suggests that there may be a more close association between the iced liver and constrictive pericarditis than has been supposed. He produced chronic constrictive pericarditis in animals experimentally and found present in the abdomen of some of his animals changes in the liver associated with a fibrinous exudate not associated with infection, and presumably due to venous stasis. The question arises whether the process, had the experiment gone long enough, would have produced a sugar coating.

Clinical Aspects. Subjective symptoms are usually of little importance. Dyspnea may be present on exertion but the patient may lie comfortably on the back. Weakness, ease of fatigue, cough, anorexia, epigastric distress and swelling are frequent. There may be no symptoms referred to the heart at all. The obliteration of the pericardial cavity with or without calcification may not cause sufficient constriction to produce symptoms or striking physical signs, and the diagnosis will turn up as a surprising one at autopsy when not at all suspected during an active life. Even when producing symptoms the evidence pointing to serious heart disease is meager. Epistaxis is not uncommon. Symptoms may be absent until introducing a progressively downhill course or may be present and remain constant or vary through a certain range for years, thus producing chronic invalidism.

The symptoms and signs occurring in chronic constrictive pericarditis have their basis in a mechanism entirely different from that of congestive heart failure and hence recognition is important because of the differences in prognosis and treatment. This mechanism is well shown in the hemodynamic studies which have been carried out by Burwell and his associates,^{7,8,9} by Beck,^{3a,4} and by Heuer and Stewart.²⁵ Congestion results from an inability of blood to enter the heart through inadequate diastolic filling rather than because of myocardial weakness as in the usual types of congestive heart failure. The heart therefore puts out less blood per beat. Measurement of the circulatory constants by the groups mentioned above shows an increased arteriovenous oxygen difference, an elevation of venous pressure, prolongation of the circulation time and diminution of the cardiac output per minute, stroke volume, and cardiac index (cardiac output in liters per square meter of body surface per minute). The total blood volume is increased.

These findings fit in well with the concept of constriction and "inflow stasis." The heart muscle is efficient and the valves not diseased, but there are reduced excursions of the heart and with exercise tachycardia is necessary to compensate for the inability to increase the stroke output. There are no remarkable murmurs. This has led Beck to include: 1, a relatively small quiet heart with, 2, high venous pressure, and 3, ascites and enlarged liver, as the triad of findings in chronic

cardiac compression. With compression and inflow stasis the venous pressure becomes elevated, followed by the results of venous stasis, as cyanosis, ascites, enlarged liver and spleen, edema, varicose veins, and hydrothorax. Cirrhotic changes in the liver develop with prolonged stasis. Burwell and Blalock⁷ point out that the high venous pressure is persistent and although it fluctuates it does not return to normal as in congestive heart failure. Intravenous infusions affect it as they do the venous pressure in congestive heart failure, with a rise in the pressure at a rate which causes no rise in normal individuals. As one would expect with reduced cardiac output systolic blood pressure is lowered as is the pulse pressure. In inspiration the blood pressure may fall, producing a paradoxical pulse. With the cardiac output per beat fixed, exercise results in excessive tachycardia.

Cyanosis of varying degrees occurs. Its mechanism has been studied by Castex, Capdehourat, and Mazzei,¹⁰ who found that it depended upon the increased arteriovenous oxygen difference produced by an increased removal of oxygen as a consequence of slowing of the arterio-capillary circulation.

Frequently there is rather marked ascites with very little and even no peripheral edema. This is not invariably true and there are patients with marked edema of the extremities. There are several reported instances¹⁵ of edema of the head and neck appearing overnight and disappearing after the patient is up and about for several hours. An adequate explanation for the discrepancy between ascites and peripheral edema is lacking. Variations in the relative increase in pressure in the hepatic veins and the inferior vena cava,^{51b} and proper relationships anatomically of the hepatic veins for stasis especially with involvement of certain parts of the pericardium,³² have been advanced as possible explanations.

There are additional cardiac findings of interest. The heart is never markedly enlarged unless there is some complicating disease. Likewise, there are no important murmurs unless, as occasionally happens, there is some other form of heart disease present.^{51b} The cardiac rhythm is usually regular but auricular fibrillation is not uncommon. Smith and Willius^{46a} found auricular fibrillation in 8 (80%) of 10 patients with adherent pericarditis unassociated with other types of heart disease. French authors⁴³ give the incidence as 33% in chronic constrictive pericarditis. In White's series auricular fibrillation occurred in 6 of 28. Paradoxical pulse occurs in varying degrees and in some series the incidence has been high. Broadbent's sign^{51a} is not seen.

A most interesting finding, with calcification, is the presence in the protodiastolic time interval of a sound which Lian, Marchal and Pautrat³³ called a protodiastolic pericardiac vibration. It is best heard at the apex or over the body of the heart. The sound occurs at the time of the physiologic third heart tone and protodiastolic gallop but differs in character.⁵³ In place of the dull thud one hears a sharp vibrating sound which is much higher in pitch. Its mechanism is not understood. Perhaps impact of the heart against surrounding structures is important.⁵³ How the calcium enters in its production is not clear. South American investigators² taking sound tracings and simultaneous phlebograms have shown that it starts after the top of the V wave during the rapid inflow phase. By such relationships it can

be distinguished from the opening snap of mitral stenosis, gallop rhythm and the physiologic third heart sound.

A summary of the literature on the electrocardiographic changes in constrictive pericarditis has recently been published by Noth and Barnes.³⁸ Electrocardiograms usually show low and slurred complexes and *T*-wave inversion simulating that of coronary disease. There may be slight right or left axis deviation and of course auricular fibrillation is not uncommon. All of these findings in whole or part may persist after operative cure. The Dieuaide test,¹⁴ which measures the change in electrical axis of the electrocardiogram with change in position of the body, has been advocated in the past as an index of fixation of the heart. Fixation by adhesions, it was thought, would prevent motion and, besides detection by physical or Roentgen ray examination, the electrocardiogram would show no or little change with the patient on the right and left side. It has been shown, however, that with constrictive pericarditis even with mediastinal adhesions the heart may be immobile, and when the heart is fixed the change in relationships to surrounding structures may account for changes in the electrocardiogram. Also in certain persons without adhesions especially with greatly enlarged hearts there may be no change with body shift.

Roentgen Ray Findings. The Roentgen ray may show normal findings in some instances, but usually is an important aid in diagnosis. Lipiodol has been used to visualize the pericardial sac experimentally in animals³⁴ but it is not attempted in diagnosis in humans. The Roentgen ray diagnosis of chronic constrictive pericarditis has been discussed in detail by Freedman.¹⁷ Fluoroscopic examination is invaluable because of recognition of respiratory changes in position and contour of the cardiac shadow and diaphragm. The fixation of the heart and thickening of mediastinal structures may be seen. Pulsations may be diminished and at times the borders hazy. Kymography is valuable in recording cardiac excursions as first shown in this country by Johnson²⁷ and may be used to follow the progress of such patients postoperatively.¹⁹ Freedman points out that in the Roentgen ray investigation of suspected cases the most conclusive sign is calcification. Lateral views may be necessary for its detection and such shadows by position may indicate the pericardial thickness, which may reach 1 to 1.5 cm. The cardiac configuration shows no or little enlargement and characteristically a triangular shaped heart. Other contours are found, however.

In summary, the chief points in the clinical picture of chronic constrictive pericarditis have been outlined by Sprague⁴⁷ as follows: 1, The patient is usually a child or young adult. 2, Ascites and hepatomegaly appear insidiously and often are out of proportion to peripheral edema. 3, Venous pressure is elevated, often to three or more times normal. It remains elevated without fluctuations seen in congestive heart failure. Femoral venous pressure may be reduced somewhat by abdominal paracentesis. 4, Dyspnea may occur on exertion but in the absence of pleural fluid orthopnea is present. 5, Cyanosis consistent with venous engorgement is present and may be intense. 6, Heart size is usually normal but moderate enlargement may be found. 7, The heart is free from murmurs of significance. Auricular fibrillation may be present. 8, Blood pressure and pulse pressure are low. Paradoxical pulse is common. 9, Broadbent's sign is absent. 10, Pleural effusions are

common. 11, Roentgen ray findings include calcification of the pericardium, limitation of cardiac pulsation, or limitation of pulsation of the right border, dilatation of the superior vena cava, dilatation of the auricles, prominence of the left upper border, and pleural thickening. Still the examination may be essentially negative. 12, Electrocardiographic findings include low voltage and inverted *T* waves of the coronary type.

Diagnosis. Importance of proper diagnosis and differentiation from the usual types of congestive heart failure lies in the entirely different form of treatment, and the good prognosis following the success of operation. There is no pathognomonic sign and one must seek out all available findings by all methods of examination, history, physical examination and laboratory.^{51b} The history of previous acute pericarditis, either wet or dry, is helpful but such a history is not always obtainable. On occasion the development of the picture from acute pericarditis is seen by one observer. The development of the clinical picture already described above, especially the evidences of congestion with increased venous pressure, hepatomegaly, ascites and little clinical evidence of heart disease on examination of the heart itself, should lead to further investigation for the important findings already given to establish the diagnosis. Other conditions producing interference with venous inflow to the heart as well as other causes of edema and ascites must be ruled out. These include congestive heart failure, polyserositis, cirrhosis of the liver and simulating lesions, inferior vena caval syndrome, and nutritional edema.

The localized hemodynamic changes of cirrhosis of the liver should clearly differentiate it. However, atrophic cirrhosis of the liver may be found associated with constrictive pericarditis. The same confusion which occurs in differentiating cirrhosis of the liver might cause difficulty with Chiari's syndrome (thrombosis of the hepatic veins), which produces a large liver, ascites, with rapid reaccumulation following tapping, as well as a number of other findings.²⁹

The inferior vena caval syndrome may be confused with constrictive pericarditis for reasons similar to those above. A normal heart would be expected. Recently there has been reported a patient²⁰ with autopsy proof of inferior vena caval obstruction showing rapidly recurring ascites, paradoxical pulse, increased venous pressure in the upper extremities as well as in the lower extremities, together with electrocardiographic changes characterized by low complexes.

Nutritional edema usually presents a satisfactory history, lowering of the blood protein, normal venous pressure, a clinically normal heart and liver, and ascites that is not as prominent as in constrictive pericarditis. Another nutritional state which could possibly cause confusion is beriberi, since minimal findings are found over the precordium with enlarged liver, peripheral edema, and ascites. However, the history together with evidences of polyneuritis, absence of evidence of cardiac constriction, and the reaction to treatment should make the differentiation a simple one. Beriberi heart without polyneuritis has been reported.¹³

Remarks concerning polyserositis have already been made and will not be repeated. With both diseases present simultaneously, the picture is confusing. Evidences of infection, the clinical aspects already described, and the differentiation of transudates and exudates is of

importance. It appears that pericardial fluids in the absence of inflammation may contain large amounts of protein,³⁵ and although aseptic and pleural fluid in transudation is poor in protein, it is not always easy to differentiate transudates and exudates.

Other cardiac states with congestion must be ruled out, particularly mitral and tricuspid stenosis. The rarity of tricuspid disease and the frequency of its association with mitral stenosis is helpful particularly if the mitral disease is evident. Tricuspid stenosis has many circulatory changes in common with chronic constrictive pericarditis.⁷ The circulatory changes rest upon an inability of blood to enter the heart, elevated venous pressure and its effects become evident, and digitalis and rest are not very helpful, because of the mechanical rather than myocardial disturbance. Mitral stenosis usually offers but little difficulty. The diastolic murmur is not seen in constrictive pericarditis, but, despite different characteristics, the protodiastolic pericardiac vibration has been confused with it. Congestive heart failure may make the murmur of mitral stenosis difficult to hear and enlargement of the heart may displace it from the usual area of auscultation. Auricular fibrillation occurs in both. However, the heart may be greatly enlarged in mitral stenosis, axis deviation in the electrocardiogram may be extreme and other evidences, such as fluoroscopic examination may help clear up the confusion when it does exist.

Prognosis. The prognosis for life varies greatly. In those developing symptoms of cardiac constriction, although the disease has obviously been present for a long time in an extremely active individual without any complaints, the course may be rapidly down-hill with death in some months. The disease is compatible with a long life, but activity may be impaired to a mild or marked degree making the individual a chronic invalid, subjected to periods of bed rest, even hundreds of abdominal paracenteses, and continual control of activities. With surgical treatment to relieve the constriction, however, if the diagnosis is adequate and if complicating disease is absent, cure may be dramatic and startling. A chronic invalid may again become a normally functioning individual. This is, however, not a blanket statement. In White's series, 11 of 28 were functionally cured by surgery. In Churchill's 37 collected cases¹¹ with decortication, of 32 there were 19 (59%) with excellent results. The mortality rate was 21.8%. Schmieden and Westermann⁴⁴ report 6 of 22 patients (27.3%) with full recovery, 6 (27.3%) markedly improved, 1 (4.5%) who died at operation, 7 (31.9%) who died postoperatively and 2 (9%) who died after transitory improvement. Some of these patients are duplications of the above series. Churchill's patients are included in the group reported by White.^{51b} Heuer and Stewart²⁵ reviewed the literature on the surgical treatment and found, as the above figures show, that although results from operation are striking, primary mortality of decortication of the heart is still high (33%), a value comparable to that of Harrington and Barnes.²¹ Of 143 cases in the literature exclusive of their own, 19 died on the operating table and 28 in the immediate postoperative period, 32.8% of the entire number, and of 135 with available data, 54 (40%) died during or soon after the operation. All of their 7 cases recovered. Of 143 there were 50 (36.6%) cured and 25 (17.4%) improved. Immediate effects, that is for several months, were striking although it may

take up to a year for full benefit to be obtained. Cures up to 18 years are on record and many patients have remained well for 2 to 3 years or more. Paessler,⁴¹ in an investigation of 71 cases, concluded that late results were not as favorable as early ones seemed to promise. He believes that improvement has in an appreciable number of cases been followed in some years by ill-health with a variety of manifestations not representing constrictive pericarditis, and he suggests that chronic constrictive pericarditis is one manifestation of a general process and that operation may not be sufficient for cure.

The high mortality appears at first to be striking, but in an incapacitating and fatal disease, improvement or cure of 60% of the patients subjected to surgery is an important record.²⁵ Also only 8 surgeons at the time of Heuer and Stewart's report in 1939 had operated on 5 or more cases, and it is expected that with better diagnosis and selection, with improvement in care and with added experience the results will improve. Benefit from surgery is to be expected only when constriction is the cause of the symptoms and when other causes of cardiac disability are absent.

Eliason and Brown¹⁶ point out that it is impossible to conceive of a pericardiectomy wound healing after constrictive pericarditis without adhesions tending to fix the heart to the sternum and surrounding structures. But these adhesions, unlike the thickened constricting ones removed, are apparently of no clinical importance. It has already been stated that adhesive pericarditis without angulation or constriction of the heart gives no important symptoms. Postoperative adhesions clinically, at autopsy, and at other operations³⁶ have been seen to produce nothing in the way of disability of the heart. In some of the patients the follow-up is not sufficiently long to ensure the absence of such a complication.

Treatment. Many factors concerned in treatment have already been given and will not be repeated. Medical treatment has little fundamental effect and is temporary. Venous pressure is not reduced to normal. Rest is helpful, but with return to exercise, the condition is aggravated and the symptoms and signs again become worse. The patient is a semi-invalid or at times is completely bedridden. Measures effective in other types of edema are helpful, for example, restriction of fluid and salts, the use of diuretics and paracentesis. Diuretics, particularly the organic mercurials, are useful and have benefited patients over long periods of time when operation has not been considered, as well as to prepare the patients for operation. Abdominal and thoracic paracenteses are helpful and often necessary procedures in preparation for operation and in carrying the patient along if operation is not done. Abdominal tapping has been done once or twice weekly for even hundreds of times.

Digitalis is not advocated by many authorities. Improvement with its use is not striking and the mechanism of production of symptoms shows why. If it reduces the pulse rate without the heart being able to compensate in its output by an increased stroke volume of blood, circulatory embarrassment would increase. With a fixed output per beat the only way the heart can increase its output per minute is by increasing the rate.⁷ Reducing the rate would be unfavorable if it dropped below the optimal level. However, it is stated⁷ that pre-

operative digitalization may be advisable, for the underworked heart which has atrophied is suddenly burdened with increased work at operation and might be usefully supported by digitalis. European workers⁴⁴ have used strophanthin in the same way. With auricular fibrillation digitalis may be beneficial.

For the surgical treatment the interested reader is referred to the recent reviews of the literature by Heuer and Stewart,²⁵ Beck,^{3b} and Harrington and Barnes.²¹ Details of preoperative preparation, operative procedures, anesthesia and postoperative care may be found there. Remarks on preoperative bed rest, restriction of salt and fluids, use of diuretics and digitalis and paracentesis have already been given.

The actual operative procedure consists of a Delorme decortication of the heart. Churchill¹¹ was the first to do this operation in this country and was followed by Beek⁴ and others until it is done quite extensively today. Resection of the adherent thickened pericardium is done and the excellent results already given above are obtained when constriction as evidenced by small pulse, increased venous pressure, small heart and other findings already mentioned are the cause. The cardiolysis of Brauer⁶ which consists of removal of some of the rigid parts of the thoracic cage to permit a retraction of the chest wall when the heart is adherent to it, relieves tugging and would be important if such tugging were important. It does not help diastolic filling from constriction, the main difficulty in chronic constrictive pericarditis.

Decortication does not always give an immediate dramatic change in the circulation in indicated cases. In Eliason and Brown's case, several days elapsed before improvement, which progressed slowly over several weeks and which in certain instances has continued up to a year. White^{51a} noted a lapse of several days before diuresis begins and the same is true of Beek's patients^{3a} in whom it has taken some days or weeks for venous pressure to drop and diuresis to take place.

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PEDIATRICS

UNDER THE CHARGE OF
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DIABETES MELLITUS IN INFANCY AND CHILDHOOD.

MANY diseases have been rendered less hopeless by the developments of diagnostic and therapeutic improvements. To many physicians, especially those whose professional life antedates the end of the first decade of the present century, the diagnosis, treatment and, consequently, the prognosis of certain diseases are at a total variance with the teaching of these conditions when they were medical students. In no disease has there been a more complete change than in diabetes, especially in childhood. In the 1909 edition of his "Diseases of Infancy and Childhood," Holt¹² devoted a scant 2 pages to the consideration of diabetes mellitus. The following is his introductory paragraph: "In this chapter will be attempted only a description of the peculiar features which diabetes presents when affecting young patients. It is a very infrequent disease in children. Of 1360 cases of diabetes collected by Pavy, only 8 were under 10 years of age. In a series of 700 cases collected by Prout, only 1 case was under 10 years of age. In a series of 380 cases collected by Meyer, only 1 case was under 10 years of age." His discussion of prognosis is also of so much interest in comparison with prognosis now that this paragraph is quoted: "In few diseases is the prognosis so bad as in diabetes in children. So high an authority as Senator declares that diabetes in children is hopeless and all treat-

ment is useless. From a study of 77 cases, Stern reaches the same conclusion. There are, however, cases on record in which recovery is believed to have taken place. The cases that I have seen have all terminated unfavorably. In a given case the prognosis, as to the duration of the disease, is rendered much worse by the presence in the urine of diacetic and oxybutyric acids. This condition is even more serious than is a high percentage of sugar; that the patient will then live more than 3 months is highly improbable."

In his 1919 edition, Kerley¹⁴ stated "True diabetes in children is, fortunately, a comparatively rare disease." Under the heading "Duration of the Disease" he stated, "Few cases live longer than a year. The majority of the cases terminate fatally in from 3 to 6 months." Under "Prognosis" he stated, "All my cases died within a year after the diagnosis was made. True diabetes is a fatal disease in children."

In his 1919 edition, Griffith¹⁰ gave a slightly more optimistic outlook when he said, "... The final prognosis in children is very unfavorable, if care is taken to exclude from the list cases not certainly diabetes, such as instances of transitory or alimentary glycosuria. Yet under newer methods of treatment the prognosis does not appear to be so uniformly bad as was formerly considered to be the case, and it would appear, as pointed out by Reisman and others, that the disease at this time of life may sometimes run a mild course and terminate in recovery."

The early advances in the treatment of diabetes are attributed by Garrison⁸ to the dietetic studies of von Noorden (1895-1911), the extensive studies of Graham Lusk (1898-1915), F. G. Benedict and Joslin (1910-1915) and the effects of the fasting treatment of F. M. Allen (1915). While some improvement in prognosis followed the dietetic treatment, the most marked advances followed the introduction of insulin and the development of a combined dietetic and insulin treatment of this disease.

In 1923 following the introduction of insulin, Strouse²⁸ in Abt's "Pediatrics" ended a consideration of some length with the following prognosis: "In discussing prognosis of diabetes in children, scientific judgment must be tempered by philosophical understanding of the difficulties of accomplishing the very exacting conditions demanded by ideal treatment. A purely scientific prognosis might be given on a theoretical supposition that all conditions of treatment can be fully met. Under such conditions, for reasons already given in the body of this study, one can say with certainty that at present the diabetic child has a decidedly better chance than he had 10 years ago. With the improved method of treatment the average diabetic child today lives longer than he did in the past decade; and if it were possible to maintain ideal conditions for a long period of time in all diabetic children, it might be possible likewise to increase the span of life considerably more. Unfortunately, however, the life of such a child cannot be lived within the walls of an institution or under the constant control of authorities. At times of delicate balance in the metabolism, the diabetic child may have to go to school or play in the street with other children. Any normal contact of this child with the world submits him to the dangers of nervous influences (excitement or worry) which might easily be the straw to break the back of his metabolism. Any normal contact with a few pennies in his pocket, may bring him to

the corner store and its alluring display of cheap candy or cake. The sugar hunger is likely to overwhelm him, and a carbohydrate spree results. Many of the children whom I have seen with diabetes have gone into coma after such carbohydrate spree."

In the more recent literature there is a more optimistic attitude towards diabetes in the young. Although there has been improvement in the situation, the child diabetic has many pitfalls that may prove disastrous. Selander²³ followed a number of cases after they left the hospital and was able to obtain reports of 155 children out of 156 treated with insulin. Of these, 27 (17.4%) had died. The morbidity during the 5-year period from 1935 to 1939 did not show a decline in comparison with the preceding 5-year period. The cause was found in an increased mortality among the group over 16 years of age, which was more numerously represented in the last 5-year period. The duration of the diabetes among those who died during the period of 1925 to 1929 was 2.2 years on an average, during the period of 1930 to 1934 on an average of 4.5 years and during the period of 1935 to 1939 on an average of 7.4 years. Coma as a cause of death was found to have decreased during each 5-year period, while tuberculosis had taken the lead during the last period as the most frequent cause of death. There were no certain complete cures observed in any case of diabetes.

McDaniel, Marble and Joslin¹⁶ studied the records of diabetic patients for the purpose of discovering any analogies between the cause of their diabetes and that produced experimentally in animals and to see if any patients could be found who seemingly were cured or had benefited by early energetic treatment. The records of those few patients were studied in whom at postmortem examination there were microscopic evidence of hydropic degeneration of the islet cells. Recent work has shown that at this stage of degeneration of islet tissue the process is reversible. The data showed that, although no cures can be claimed, early, vigorous treatment in certain patients with a restricted diet or insulin or both seemed to have brought about an unexpected degree of improvement. Many other patients, treated in a like manner, responded with only the expected improvement. Resting procedures, such as fasting, fat feeding and insulin, prevent the degenerative changes from occurring in cells not already affected and permit the restoration of those exhausted cells, which still retain the ability to recover. They feel that diabetes is never complete until death occurs as there are always some functioning islet cells and to keep them in a functioning state is the main goal of treatment. It is their policy to begin vigorous treatment with insulin and a low carbohydrate diet with the required calories made up in fat. If, after a few weeks, there were no signs of improvement they would increase the diet to one of moderate carbohydrate restriction, assuming that by this time all beta cells which could recover had done so. They would be extremely slow in reducing the insulin dosage and diligent in its use with intermittent infections. They believe that the diabetic patient should be taught to guard his islet tissue as he does his toes and limbs.

The presence of sugar in the urine is not necessarily evidence of the presence of a true diabetes. Bayer and Davis² stated that it is especially difficult to rule out diabetes in children. Since the variations of blood sugar in the normal child are so great, normal readings are not

always a guarantee of normal sugar metabolism. It is unfortunate to view too gravely a repeated glycosuria of dubious significance. They presented a series of cases which gives support to the optimistic outlook with regard to the prognosis of children with atypical glycosuria. Between 1923 and 1938 some 50 children passed through the pediatric ward of Stanford University School of Medicine with a diagnosis of possible diabetes mellitus. The glycosuria of 9 of the children was either considered non-diabetic or called diabetic with definite reservations on the part of the staff. In the spring of 1939, from 2 to 11 years after the original diagnoses were made, it was possible to recheck every one of these 9 patients. It was found that only 1 of them was diabetic.

Goettseh and Mason⁹ reported a case of lead poisoning with glycosuria. They carried out studies on this patient which showed that the height of the blood sugar was consistently normal or lower than normal and that the urinary concentration of sugar remained relatively constant irrespective of the diet. The glycosuria persisted for 5 weeks, and the concentration of urinary sugar fell as convalescence progressed. The studies were compatible with the suggestion that the condition in lead poisoning should be classified as a renal glycosuria. This is supported by a survey of 8 cases of lead poisoning with glycosuria in children. In 5 of these cases, in which determinations were made, the blood sugar values were normal. In 3 cases, in which dextrose tolerance curves were obtained, the curves were not of the diabetic type.

The question naturally arises as to what are the normal blood sugar values in children. Rudesill and Henderson²² made 288 blood sugar determinations by the Folin-Wu method on 144 non-diabetic children from 2 to 15 years of age. They made readings on both the fasting specimens and those made at 11 A.M. on the same day. They found that there was no practical difference in the blood sugar values. By the Folin-Wu method normal fasting blood sugar values in non-diabetic children was found to be from 70 to 105 mg. per 100 cc. They felt that the values for the normal amounts of fasting blood sugar was of the greatest usefulness in the study and treatment of diabetes mellitus. Since slowly acting insulins have come into general use, there are more often needed figures for normal limits as a guide in therapy. In order to know the normal blood sugar level in a child, the normal upper and lower levels must be known. The range of normal values can be safely considered to be between 50 and 110 mg. per 100 cc., but probably it should be placed between 60 and 100 mg. per 100 cc. since practically all values are found to be within these limits. Levels for children between 2 and 15 years of age had the extreme range of 52 to 115 mg. per 100 cc., but there were only 5 instances in 288 tests which did not fall between 70 and 105 mg. per 100 cc. While an occasional value may be reported as slightly lower or slightly higher than these figures, it is a comparatively rare exception since 98% of these readings were between 70 and 105 mg. per 100 cc. These observations also showed that blood sugar values determined $3\frac{1}{2}$ hours or longer after meals may be substituted for fasting blood sugar values in clinical practice.

McKittrick¹⁷ made determinations of values for blood sugar for 73 normal newborn infants and 1 infant of a diabetic mother. During the first week of life low values were found. The lowest point was reached by the average baby on the third day. Values for blood sugar

above 40 mg. per 100 cc. were regarded as normal in the first week of life. During the second week the range was found to be from 60 to 120 mg. with the average between 80 and 90. During the first 2 weeks of life a gradual elevation of the level of blood sugar occurred, with a decrease in the spread of the maximum and minimum extremes. The blood sugar regulating mechanism of the newborn infant is unstable and undergoes an alteration towards greater stability during the first 2 weeks of life.

Diabetes is classed as one of the familial diseases. For this reason the children of diabetic parents are expected to inherit the tendency to have this disease. As far as the newborn is concerned the opposite state is sometimes observed during the neonatal period. Smyth and Olney²⁵ studied 19 infants born of women whose pregnancy was considered to have been complicated by diabetes. In 14 of the mothers glycosuria appeared only with gestation and was controlled by diet or by diet and the temporary use of insulin. This suggested that the glycosuria was from other causes than diabetes. Of the entire group, 11 gave birth to excessively large infants. The infant's blood sugar, even allowing for predelivery insulin, was low. In 2 of the infants projectile vomiting and cyanosis were striking features, and these were doubtless related to persistent hypoglycemia. The use of subcutaneous glucose was extremely valuable in carrying the infants through the critical period until an apparent adjustment was made. A follow-up of 1 patient showed a hyperinsulin-like sugar curve at the age of 4 years. The reports of postmortems of infants born of diabetic mothers vary. In some no hyperplasia of islet tissue has been found, and the hypoglycemia must be considered functional in type. In others, the finding of hypertrophy and hyperplasia of the islets of Langerhans explain the hypoglycemia. The relative macrosomia, advanced bone age and more mature genital tract suggest a pituitary effect. Complete endocrine pathologic study was reported but the interrelationship was best described as dysfunction. Perhaps some interrelationship will be found to account for the mild as well as the fatal hypoglycemia of the newborn infant.

Miller and Ross¹⁸ stated that the belief is widely held that the hypoglycemia of newborn infants, whose mothers have diabetes, is the cause of the cyanosis, muscular twitchings, convulsions and occasionally the death of the infant. They question whether or not the hypoglycemia so frequently observed in these infants is as significant in the production of symptoms as is generally supposed. They stated that, without more facts than are at present available, a discussion of the effect of hypoglycemia on the newborn infant must be largely conjectural. There are two outstanding facts. Low concentrations of blood sugar are to be expected in infants of diabetic mothers, and difficulties seem to occur more frequently in these infants than in those whose mothers do not have diabetes. Occasionally they found low concentrations of blood sugars in infants who presented no abnormal findings in the neonatal period and whose mothers did not have diabetes. The average blood sugar concentration in infants born of diabetic mothers was significantly lower than in normal full term infants. However, the blood sugar concentration in some full term babies was as low as that of infants of diabetic mothers. In normal premature infants the blood

sugar readings were practically the same as those of infants of diabetic mothers. The low blood sugar level in normal infants did not, as a rule, produce symptoms as these infants seemed to adjust themselves to the low concentration.

Sisson²⁴ pointed out that the infants of diabetic mothers showed a high morbidity and mortality rate. He studied 65 consecutive cases of infants, whose mothers had diabetes. He remarked that such a group of infants was non-existent two decades ago before the insulin era. Women with diabetes either did not become pregnant or failed to give birth to a living child. Since the use of insulin the fecundity of the diabetic woman has increased greatly and the juvenile diabetic patient has reached the childbearing age. For these reasons there are increasing numbers of pregnant women with diabetes mellitus and consequently an increasing number of babies of diabetic mothers. Diabetic mothers still have a large number of miscarriages and stillbirths. There has been a great variation in the mortality rate and in some reports the rate has been as high as 40%. Another observation has been that these babies are unusually large so that they are frequently called "giant babies." There has been no evidence that the skeletons of such babies are larger than normal or that the babies develop into larger types. Another conception from previous studies has been that these infants are frequently born with hypertrophy of the islands of Langerhans. Recent work has shown that the majority of the infants studied have this condition, although it may also be found in normal infants. This series of 65 infants of diabetic mothers was divided into three groups. The first group consisted of 37 babies who were normal at birth and whose course during the neonatal period was uneventful. This group included a few infants who were somewhat sluggish in breathing and who had minor degrees of cyanosis, but who were not thought to be different from a great many babies usually regarded as normal. It was found that 35% of this group were born of mothers who had diabetes for from 10 to 20 years and that 78% of them were delivered by Cæsarean section. Also 86% were delivered between the eighth and ninth months of gestation. The second group consisted of 16 infants who survived but who presented definite major symptoms, which generally occurred directly after delivery. These symptoms were not uniform, but were primarily respiratory with depressed reflexes and difficulty in eliciting crying. These symptoms usually persisted for the first 24 hours and rarely lasted more than 2 days. Oxygen usually improved the condition but parenteral dextrose was without much effect. In this group of 16 infants 31% of the mothers had diabetes for from 10 to 20 years. About a third of the mothers showed definite signs of preëclampsie toxemia with elevation of blood pressure, edema and albuminuria. Cæsarean deliveries were made in 50% of this group and all were born between the eighth and the ninth months of gestation. None of these infants were of abnormal size. The third group consisted of 12 infants of diabetic mothers who died within the first 3 days of life. There was a great variation in the symptoms and there was no common cause of death. The mortality rate was 18%.

The question of heredity in the etiology of diabetes is one that has received a great deal of attention. Hildegard Thén Berg²⁵ in Munich has been making a study with a basic material of some 85,000 diabetics

among whom there were 411 pairs of twins. In 147 of these pairs she found that 46 were enzygotic and 87 were dizygotie, while the exact zygotie origin of two pairs was open to question. Twelve pairs were found not to have diabetes. A pair of twins was termed absolutely concordant if each twin of the pair was at the time of the examination suffering from a manifest diabetes mellitus with demonstrable excretion of sugar in the urine. If 1 twin, although not manifestly ill and passing normal urine, showed by the tolerance test that the insular system was unable to metabolize a tolerance test dose of twice 20 gm. of dextrose, the pair was termed concordant according to tolerance. A group called discordant according to tolerance was also distinguished. Among these the dextrose tolerance test of the twin who was not manifestly ill revealed a normal blood sugar curve, which, after fasting, was not above 120 mg. per 100 cc. This curve at its peak did not exceed 180 mg. per 100 cc. After 40 minutes in the second tolerance test with dextrose it showed no further rise, and finally, after 120 minutes, it returned to normal. Termed probably discordant were those twins who could not be examined because they had already died but who, according to the histories of their cases, appeared not to have been affected with manifest diabetes mellitus. According to this part of her study 17 pairs of enzygotic twins were absolutely concordant, 13 were concordant according to tolerance, 6 were discordant according to tolerance and 10 were probably discordant. Of the dizygotic twins 9 pairs were absolutely concordant, 9 were concordant according to tolerance, 32 were discordant according to tolerance and 30 were probably discordant. The author is thought to have proved on this large group of twins that diabetes mellitus was purely hereditary.

Fischer⁷ stated that diabetes was rare in twins, especially in childhood, and that the opportunity to study the non-diabetic twin rarely presented itself. He claimed that his presentation was the first of this type to be described. It was expected that the non-diabetic twin would show a decreased tolerance for dextrose. She was studied 3 times. The first curve was obtained soon after the diabetes was observed in her twin. The second was made about a year later after an infection and showed a decreased tolerance for dextrose. This might have signified impending diabetes but on repeated examinations the urine showed no dextrose. The last curve was made some 3 years later and was normal. From statistics it might be expected that this member of the pair will manifest diabetes later although there has not been any evidence to the effect as yet other than a temporary decrease of dextrose tolerance after an infection.

Brown and Thompson⁸ made a study on the data pertaining to body growth, intelligence, heredity, sex distribution and incidence of acute infections of 60 juvenile diabetic patients. The group of patients included in this study appeared to be typical of the juvenile diabetic population of Minnesota and apparently representative of the general child population of the state as regards socio-economic status, race and geographic distribution. While one-third of the patients reported having had some acute infection other than the common cold within 6 months of the onset of diabetes, the group, on the whole, was as healthy as the non-diabetic siblings except for acidosis and insulin reactions. Limited measurements of this group revealed no consistent

or peculiar deviations from the average in height. The diabetic children were significantly underweight only during the first 6 months of their disease. In contrast to the superior intelligence shown by Joslin's diabetic children, the intelligence of this group showed no deviation from the average and no significant deviation from that of the control group of non-diabetic children or from the average of Minneapolis children. There were no characteristic abnormalities in personality.

According to White^{30b} the search for clinical evidence of endocrine imbalance in juvenile diabetes has become imperative because the results of present-day physiologic research indicate that experimental diabetes is a disturbance of endocrine regulation. The importance of these investigations rests not only with the fact that from the combined data of the laboratory and the clinic the mechanism of diabetes may be explained and its cause and prevention indicated, but also with the possibility that a more nearly perfect form of treatment may be developed. She presented data on 1250 patients with juvenile diabetes. The onset of the disease had occurred prior to the age of 15 years. In this group, there were 177 patients who showed prolonged hypophyseal involvement. Of the 177 patients, in 176 the anterior lobe of the hypophysis was concerned. Of these, 9 showed evidence of hyperactivity and 168 had manifestations of hypoactivity. Among these patients were 94 dwarfs, 22 with Froelich's syndrome and 51 with signs of infantilism. Only 1 patient had signs and symptoms related to the posterior lobe of the hypophysis. None of the 1250 patients showed signs of deficiency of the thyroid gland, but 3 had signs of hyperthyroidism, 1 had possible adrenal disturbance and 28 had lesions related to the gonads. All presumably showed hypofunction of the pancreas, but 2 presented signs of hyperinsulinism in addition. Disturbances of the liver were noted in 65. This may or may not have been endocrine in origin. The juvenile diabetic patient showed evidence of a disturbed hormone balance. There was striking evidence of hyperactivity of the pituitary body in the pre-diabetic stage, followed by diminution of activity which in its most extreme form occurred in the diabetic dwarf.

The effect of a preceding injection of diabetic blood as compared with normal blood on the response of the rabbit to insulin was studied by de Wesselow and Griffiths.⁵ The animals were starved 18 hours before the experiment. Inspection of the curves showed that after injection of 10 cc. of plasma obtained from 9 non-diabetic middle-aged subjects and 7 young diabetic patients, all but 2 of whom had been receiving insulin for some time, there was no appreciable alteration in the form of the blood sugar curve during the period following the injection of insulin. In the case of 16 elderly diabetic subjects with abnormally high blood pressure, the majority of whom were overweight and of whom only 3 were receiving insulin, it seemed that a preliminary injection of the plasma into the animals resulted in an early arrest of the fall in blood sugar after insulin. Associated with this premature arrest there was a very definite tendency for the blood sugar to be higher than the control values during the remainder of the experiment. This effect of a diminished fall and a more rapid restoration of the blood sugar after the injection of plasma of these patients was particularly evident in 6 of these 16 patients. During the second period of 30 minutes following the injection of insulin the blood sugar had already

begun to rise and after 60 minutes the average blood sugar exceeded the initial value. In these respects the curves obtained after injection of plasma were in sharp contrast to those of the first two groups of patients. The conclusion was that the blood plasma of some elderly, obese, glycosuric patients was found to diminish the hypoglycemic action of insulin in a manner closely resembling that observed by other workers with extracts of the anterior pituitary gland. They felt that the knowledge of the metabolic disturbances in diabetes would undoubtedly be considerably extended as the thesis that the anterior pituitary gland and the pancreas act antagonistically in the control of carbohydrate metabolism is developed. Any alteration in the balance of those opposed influences must lead to abnormal carbohydrate metabolism.

Aside from the dysfunction of the pancreas, the other endocrine glands participate in the metabolic disturbances of diabetes mellitus and complicated regulatory hormonal mechanisms, which are controlled by the vegetative nervous system, are present. In experiments on animals, true diabetes can be produced by injection of prehypophyseal hormones. Strauch²⁷ reported a very instructive case which throws light on the mutual relations between the hypophysis and diabetes mellitus. This patient was 17 years of age and had suffered from exhaustion, bad memory and retardation of growth for 2 years. Examination showed underdevelopment, flaccid musculature, and accumulation of fat, especially in the lower part of the abdomen, hips and thighs. The structure of the body was normal without any feminine traits and the patient was normal psychically. The internal organs were normal. The genitals were very small and axillary and pubic hairs were completely absent. Treatment was started with testicular preparations but resulted only in diminished exhaustion and improved temper. No improvement of the other pathologic signs could be obtained. Prehypophyseal treatment was then instituted. Within 1 month the pubic hair began to grow and the fat accumulations diminished in size. Within 6 months the patient grew 5 cm. and his school work improved considerably. Six months after the beginning of treatment, excessive hunger and violent thirst appeared and soon afterwards sugar and acetone were found in the urine. The patient complained of exhaustion, restlessness and irritability. On admission to the hospital a blood sugar value of 326 mg. per 100 cc., 4.8% of sugar in the urine and large amounts of acetone and diacetic acid were demonstrable. A typical precomatose condition with cardiovascular disturbances was present and could be controlled by administration of insulin and glucose. Within 2 weeks the urine became free of sugar and acetone and the blood sugar decreased to 150 mg. per 100 cc. with 8 to 10 insulin units per day. The author thought that the diabetes mellitus in this case was produced by the hypophyseal hormone which had been successfully administered for the dystrophia adiposo-genitalis. No suspicion of a pre-existing latent diabetes was present in this case. Care should be taken in administering vitamins and hormones which are not indifferent and they should be used only where there is a definite indication. From this case it is seen that there is a close relationship between diabetes mellitus and the hypophysis.

Steiner and Newcomb²⁸ observed that the association of hyperthy-

roidism with juvenile diabetes mellitus brought about a striking change in the diabetic state. The effect of hyperthyroidism on carbohydrate metabolism was well illustrated in one of the cases of their series. Because of the family history it might be suspected that these changes were the result of a diabetic tendency or of latent diabetes activated by the hyperthyroidism. It cannot be denied that this may result, yet careful study and prolonged follow-up of these cases are necessary before a definite diagnosis can be made. Interesting improvement followed in dextrose tolerance after the patient was made to rest and was given a high calorie diet and iodine was administered. This improvement would not have occurred without the use of insulin if diabetes had been a complicating factor. The differentiation of diabetes and hyperthyroidism is sometimes difficult and the hyperthyroidism may be overlooked. For this reason it is a wise procedure to have the basal metabolism of every diabetic subject and every hyperthyroid case should have a sugar study. There is a great similarity of the cardinal symptoms of the two diseases. Polyphagia, polydipsia and the loss of weight and strength are common to both. Sugar is frequently found in the urine of patients with hyperthyroidism and hyperglycemia is fairly common. The mechanisms of glycosuria and hyperglycemia are different in the two diseases. Patients with hyperthyroidism have glycosuria, postprandial hyperglycemia, impaired dextrose tolerance, a low respiratory quotient in the fasting state and depletion of the glycogen of the liver. These suggest diabetes mellitus. There are other physiologic findings which aid in the differentiation. The utilization of sugar by the tissues is increased. The arteriovenous blood sugar difference is normal or increased in spite of an increased rate of blood-flow. After a carbohydrate meal the rise in the respiratory quotient is higher and the fall more rapid than normal. The fall in the level of inorganic phosphates of the blood is normal. This is caused by the formation of a hexose phosphate compound in the process of utilization of dextrose by the tissues. On the other hand, in diabetes mellitus there is a reduced capacity to utilize sugar and the arteriovenous blood sugar difference is less than normal. As a result less sugar is taken up by the tissues. After a carbohydrate meal the respiratory quotient remains low, and the fall in the level of inorganic phosphates of the blood following an increased supply of carbohydrates is less than normal. When the two diseases coexist the diagnosis of diabetes mellitus is usually made first. Certain features during the course of the illness should arouse the suspicion that disease of the thyroid gland may be a complicating factor. Inability to control the glycosuria and the hyperglycemia with regulation of the diet and with what should be an adequate dosage of insulin are significant findings. Acidosis is prone to develop in these patients, especially if they are losing weight or are undernourished. Rapid pulse, restlessness, flushing, moist skin and tremor of the hands all aid in making the diagnosis of hyperthyroidism particularly in younger patients.

Cuttle⁴ pointed out that diabetes mellitus in the young differs from the disease in the adult. The onset is abrupt and violent. The disease is more severe than in adults. It is usually progressive and it is more labile than in adults. There is a more definite relationship between juvenile diabetes and hyperfunction of the anterior lobe of the

hypophysis than is the case in adults. The condition is not usually preceded by obesity or by degenerative changes. In planning the treatment of diabetes these peculiarities should be taken into consideration. There should be adequate nourishment. A level of blood sugar below 200 mg. per 100 cc. should be established. There should be less than 10 gm. of dextrose in the urine in 24 hours. The cholesterol content of the blood should be below 230 mg. per 100 cc. There should be normal psychological adjustment and development. The psychologic adjustment of the child to the limits imposed by the disease may present a difficult problem. He must be taught the nature of his disease, its dangers and his part in the control, while at the same time he is educated to live happily with his disease.

White^{30a} stated that in general the apparent difficulty in the management of juvenile diabetes has two explanations. The disease is uncommon in childhood. Therefore, unless the physician is especially interested in diabetes he sees few children afflicted with it and consequently he lacks experience. Then also since the commonest age of onset of diabetes is that of 12 years, the child is rarely treated by the pediatrician, whose mind should be unbiased, but more often by the general practitioner or physician who is accustomed to deal with diabetic adults and expects to find the same mental attitude in the young patient and applies the same standards for control and the same principle of treatment. Even the type of onset is characteristic, for in the child the disease is acute and virulent. Often the first recognition is made in the chemical coma, and the younger the patient the more striking is this fact. In the George F. Baker clinic the calorie requirement is based on surface area. Since in childhood this follows age closely, calories may be prescribed accordingly—1000 calories to an infant of 1 year with 100 calories added for each year of life. For girls a maximum of 2200 calories is reached at the age of 13 years. As soon as possible after maturity, the calorie prescription for girls should be reduced to avoid the obesity common in female adolescents. The maximum caloric diet prescribed for boys is 2800, a point reached at the age of 19 years. The ratio of carbohydrate to fat is selected according to one of two methods. Those who believe that stimulation of the pancreas results in improvement of diabetes prescribe carbohydrate-rich and fat-poor diets. Those who believe that rest of the pancreas is beneficial, prescribe low carbohydrate diets. All diabetic children require insulin and should be given it from the day that the disease is recognized and preferably continuously. After 3 years' experience with protamine insulin it is believed that this is the ideal form to use in the treatment of juvenile diabetes. However, unlike adults of whom 50% require no regular insulin in addition to the protamine insulin, it is found that 90% of children will require both regular insulin and protamine insulin. These should be given in separate injections simultaneously before breakfast.

Using a constant regimen of treatment for a selected group of children with diabetes mellitus, Jackson, Boyd and Smith¹³ continued detailed hospital control until stability of insulin requirement and normal range of fluctuation in blood sugar have been attained. The regimen employed has been based on the premise that physiologic levels of control such as normal blood sugar levels, freedom from glycosuria or insulin

shock and complete adequacy of diet are desirable and attainable. They found that with strict hospital and laboratory control, a period of 6 weeks to 2 months was necessary to attain suitable stability of the sugar-handling function. Adequately prolonged hospital control of the patient at the outset of his management increased his subsequent stability under home management and avoided the difficulties which characterize the treatment of the diabetic child. With the establishment of such stability the insulin requirement became much smaller than during periods characterized by mild glycosuria or hyperglycemia. In view of this spontaneous lessening of the insulin requirement many studies that are reported as to the relative value of different types of insulin are open to question as to the conclusions that are drawn. Probably few children with diabetes mellitus in the country at large attain a desirable level of control, especially when preliminary stabilization is not complete and mild glycosuria is so frequently allowed. With improvement of level of control the authors predicted that there would be a lessening of complications, sequelæ and fatalities.

Herron¹¹ found that in managing diabetes in children one must take into consideration the growth and education of the child as well as the severity, instability and progression of the disease. The ideal was to produce a normal blood sugar throughout the 24 hours without shock or glycosuria and to produce normal growth and allow a happy existence. Individualization of dosage was necessary and was based on frequent determinations of the blood sugar and urinalyses. Hospitalization was recommended for new patients until the proper routine was established. Juvenile patients responded to protamine zinc insulin unusually well. It was found that a diabetic child cannot have a normal diet without insulin and he will not adhere to an inadequate diet. Most children do best on a high carbohydrate-low fat diet, because of the better metabolic balance. They show less tendency to go from hypoglycemia to hyperglycemia, a lowering of the insulin requirements in many cases, better adherence to the diet, an increase in carbohydrate tolerance and an increase in weight, strength and energy. A weighed diet was urged for the best control of the disease. Proper control allows normal growth and development and a happy existence.

Möllerström¹⁹ expounded his ideas concerning the selection of food for diabetic patients, based on an experience with over 1000 cases. Illustrating the extremes to which non-physiologic thinking has led some authorities he pointed out Lundberg's advocacy of large amounts of vegetables and alcohol for the treatment of the acidosis in adults. Certain deficiency syndromes result from the fantastically one-sided diets that have enjoyed popularity. The pediatrician first introduced more physiologic diets. The need of an ample amount of carbohydrate is important. Since it seems that ketosis can follow from the incomplete conversion of carbohydrate to fat as well as from B-oxidation of fat, excess of carbohydrate may be harmful. It must be borne in mind that hyperalimentation is harmful, but starvation may precipitate grave dangers. Of these ketosis is the chief hazard. The metabolic consequences of hyperglycemia and glycosuria without acidosis are questionable. Although it is usually assumed that the atherosclerosis which so frequently accompanies diabetes in elderly people is a consequence of diabetes, it is also likely that the mildly diabetic state repre-

sents a defense mechanism to supply more dextrose to the undernourished myocardium. Although this may seem a novel concept it is supported by clinical evidence. The result may be that zealous treatment of the diabetic symptoms may exaggerate the myocardial inadequacy. As a general thing the effect of a given amount of insulin is significantly increased when its administration is timed in relation to the patient's endogenous rhythm. This rhythm is more clearly followed by studies of the diurnal fluctuations of acid formation than by studies of the urinary and blood sugar. The patient's own appetite should be one index of his requirements and should not be disregarded by prescribing a rigid, unvarying fare. There should be essential difference between the diet suitable for the child and for the adult diabetic.

Nelson and Ward²⁰ reminded us that prior to the introduction of insulin diet was the sole factor in the treatment of diabetes mellitus. The principle of treatment in the later portion of the pre-insulin period was induction of marked malnutrition and employment of diets high in fat and low in carbohydrate. Since 1922 there has been trend towards the use of normal or average diets. The aim of treatment of diabetic children has changed from mere prolongation of life to maintenance of adequate growth and normal activity. Although there have been distinct differences of opinion regarding the qualitative and quantitative content of the diet, the tendency has been towards a more liberal allowance of carbohydrate. The types of diets generally used include low carbohydrate and high fat; moderate carbohydrate and high fat; moderate carbohydrate and moderate fat; high carbohydrate and low fat; high carbohydrate and moderate fat; limited carbohydrate with other portions unlimited, and an entirely unrestricted diet. These groups overlap. Numerous advantages are claimed for the higher carbohydrate diets. Among these are the lower cost, its greater palatability and especially its approximation to the average diet so that all the members of the family may partake of it. This last point is an important one in the treatment of children. The actual efficiency of the diet is often measured in terms of the units of insulin required to balance it. The authors did not advocate the use of free and unrestricted diets, but felt that a more normal type of diet may be used than is sometimes advised. In favor of the use of measured diets the most important factor is the control of weight while others are the assurance of a balanced intake, instruction of the child by experience with the content of an adequate diet, reasonable distribution of the diet through the day and the psychologic effect of aiding the training of the child in self-discipline. This last factor is important but it is effective only so long as the child is given an ample diet. Diabetic children cannot be expected to adhere to inadequate diets.

Lichenstein¹⁵ pointed out that those with experience in pre-insulin days remember the terrible existence that diabetic children had to sustain. The extremely strict diet supplied to these unfortunate children scarcely contained anything that could appeal to the taste of children in general. In spite of all privation the result of the strict diet always became unfavorable after a very short while. With the introduction of insulin new therapeutic prospects were opened. The new remedy gave the possibility of supplying a more liberal diet as well as

of meeting the risks of infection with more confidence and of overcoming the state of coma in a new way. It would have been possible earlier to have taken full advantage of the introduction of insulin. At first it was used as an auxiliary to a strict dietetic treatment, which was regarded as the main point. It still is regarded as the main point by many. The children still have to endure a restricted existence. They have not been allowed to enjoy the pleasure of satisfying their hunger in a normal way and they have still been treated as exceptions, which has been anything but advantageous especially as regards their psychical development. By degrees the views on this matter have changed. More and more the conclusion has been reached that children suffering from diabetes should be allowed to lead as normal existence as possible. The author has been using the free diet for several years and he has emphasized in his teaching the importance of letting the diabetic child have a chance of living a normal life with free choice of food buffered by a sufficient dosage of insulin. He defined free diet as an absolutely free diet without any restrictions and without weighing the food or any of its ingredients. In other words, the children are allowed to satisfy their appetite and to some extent their individual taste. The only restriction is the avoidance of luxury, which also ought to be avoided by normal children. The insulin is given in doses sufficient to keep the child in good general condition, in good increase of weight and free from ketone bodies in the urine. There is little importance to be attached to a somewhat greater or lesser sugar excretion provided the increase has not appeared in connection with a change for the worse in the general condition of the child or in the weight curve. The change from the restricted to the free diet has always been an easy one. The patients themselves and their families appreciate the release from strict dietary schedules and from the daily trouble of weighing and measuring the allowed quantity of food. There is a great joy on the part of the diabetic child at the release from the strict dietary regimen and when this has been seen it is possible to appreciate the altered psychologic condition from being placed in a method of living similar to that of normal children. This gives a favorable influence on the disease.

It was found that as a first result of the change the children showed a voracious appetite for carbohydrates. Very soon the child passed on to a more normal consumption of carbohydrates which varied but little. The supply of carbohydrates remained on a higher level than previously. Any inconvenience on account of the increased supply of carbohydrates was not observed. On the contrary, the condition of the patient was always influenced favorably by the change and often to a great extent. Even the weight curves manifested improvement, depending on the fact that not only the supply of carbohydrates but also the total supply of calories increased. It might be expected the blood sugar level, as well as the carbohydrate excretion, would be increased if the insulin dosage was not raised correspondingly. This was not the case. Although some patients on free diet have required larger doses of insulin than previously, the increase has usually been moderate and sometimes insignificant. In many cases the dose of insulin was maintained unchanged without inconvenience, and in some cases it was possible to reduce it, in spite of the fact that the supply

of carbohydrates was twice the amount previously given. The blood sugar level often proved to be more regular than before, sometimes a little higher, but sometimes considerably lower, and at the same time more uniform. The urinary sugar excretion has not been considerably higher during the free diet, but sometimes remarkably low in proportion to the large supply of carbohydrates. One inconvenience attached to the free diet was that when using regular insulin three injections must be given in 24 hours. However, when protamine insulin was used instead of the regular insulin it was possible to reduce the dose to even one per day in spite of keeping the child on the free diet. On free diet the danger of overdosage of insulin with its consequent trouble was far less. Another interesting fact was that the ketonuria disappeared or decreased considerably after the change to the free diet. This meant that the danger of coma was reduced. Because of this as well as because of the other advantages the return of the patients for hospitalization was avoided.

Feinblatt⁶ made a comparative study of standard insulin, crystalline insulin, protamine insulin and hexamine insulin. He found that low blood sugars were maintained several hours longer on the crystalline insulin than on standard insulin. The unit value of protamine insulin was found to be greater and more lasting than the unit value of standard insulin. Another favorable finding was that under this form of insulin there was an absence of ketonuria and decreased incidence of lipemia. The introduction of protamine insulin was a great advance in the treatment of diabetes as the practicality of a single daily injection encouraged both the patient and the physician to favor insulin therapy. A later modification was hexamine insulin. This is a compound of insulin and hexamethylene tetramine. This form is also used in a single dose. In this study it was shown that the blood sugar curve could be kept at a lower level than with protamine insulin and with smaller fluctuations during the day. There was also the striking absence of ketonuria. This insulin was also found to have the specific effect in decreasing polyuria in those patients who complained of it under standard insulin and under protamine insulin.

Alpert¹ offered a new therapy by combining protamine insulin and hexamine insulin. He stated that when these were mixed in the same vial they retained their individual characteristics as is evidenced by the blood sugar time curves. The hexamine insulin gave an immediate as well as some intermediate blood sugar lowering effect, while the delayed action of the protamine insulin was preserved. The use of the combined hexamine and protamine insulins eliminated the necessity for supplementary injections of insulin during the day. In the mixture of these two insulins the hexamine insulin remains fluid while the protamine remains a precipitate.

The most frequent complication of diabetes is tuberculosis. Noblecourt, Ducas and Scheinmann²¹ pointed out that among adults it has been found to be the chief cause of death since the introduction of insulin has reduced deaths from distinctly diabetic causes. Before the use of insulin the short course of diabetes in children, which averaged about $2\frac{1}{2}$ years, prevented the evolution of coincident tuberculosis, but since the introduction of insulin this complication has been found in many juvenile diabetics. When a diabetic child becomes tuberculous it is

of interest to observe the influence of the tuberculosis on diabetes and the influence of the diabetes on tuberculosis. As regards the influence of tuberculosis on diabetes, it has been recognized that in the adult tuberculosis aggravates the disequilibrium of the glucosides, favors the onset of acidosis and establishes a relative resistance to insulin. In the child the effect was found to be similar but much less marked. A rigid dietetic regimen was recommended to avoid disaster. The rôle of diabetes in the evolution of tuberculosis depended on the therapy that was instituted. Sometimes diabetes preceded the appearance of tuberculosis. They believed that in diabetic children tuberculosis had an acute onset.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 10, 1941

Synthesis of an Isomer of Corticosterone. MAXIMILIAN EHRENSTEIN (Cox Institute, University of Pennsylvania). Recent evidence points to certain physiologic differences between desoxycorticosterone and corticosterone. Both substances occur in adrenal-cortical extracts. At present only desoxycorticosterone has been obtained by synthesis. Corticosterone differs from desoxycorticosterone in that it has a secondary hydroxyl group attached to carbon atom 11. The synthesis of

corticosterone itself appears extremely difficult. We were successful, however, in synthesizing the acetate of an isomer of corticosterone which has one hydroxyl group attached to carbon atom 6 instead of carbon atom 11. It remains to be seen how far the physiologic action of this substance differs from that of corticosterone and desoxycorticosterone.

21-Acetoxy-pregnenonol which can be synthesized from cholesterol served as starting material for this investigation. By treating it with perbenzoic acid a mixture of (5:6)-oxides was obtained which contained mainly the α configuration [Pregnane-(5:6) (α)-oxide-20-1-3,21-diol 21-monoacetate]. The oxide ring of this substance was ruptured by means of glacial acetic acid with the formation of a 6-acetoxy-compound. [Pregnane-20-1-3,5,6,21-tetraol 6,21-diacetate.] To a minor extent acetylation took place also at carbon atom 3. The main product of the reaction was subjected to an oxidation with chromic acid which furnished Pregnane-3,20-dione-5,6,21-triol 6,21-diacetate. Dehydration of the latter substance by means of dry HCl gas in a solution of chloroform yielded the diacetate of 6-Hydroxy-Desoxycorticosterone.

Apparatus for Recording Cyclical Activity in the Rat and Correlation of Leukocyte Count With Peak of Estrus.* EDMOND J. FARRIS (The Wistar Institute of Anatomy and Biology). A new apparatus was designed to register the number of revolutions of a turntable per unit of time. The revolutions of turntables in rat cages are registered on magnetic counters mounted on a panel in another room. The counters are photographed on the hour for continuous 24- or 48-hour records, by time-lapse mechanism. The apparatus is accurate for determining peak, regularity and length of estrus cycle. The system of cages and apparatus is arranged to reduce handling of animals to a minimum, and consequently neurophysiologic (emotional) stimulation is practically eliminated, for the animals are handled only once a week.

It was found that with peak of activity there was a leukopenia and during the diestrus interval, a leukocytosis. Constant darkness activity records were discussed.

Motion Picture Showing Chemotaxis of Leukocytes. D. R. COMAN (Department of Pathology, University of Pennsylvania). A moving picture of rabbit polymorphonuclear leukocytes, showed the chemotactic responses of these cells to various substances. Positive chemotaxis to collodion, negative chemotaxis to a silicate and random motion (indifferent chemotaxis) to carbon, were shown.

The Quantitative Measurement of Cerebral Blood Flow in the Monkey. C. F. SCHMIDT and P. R. DUMKE (Department of Pharmacology, University of Pennsylvania). Quantitative measurements of

* This investigation was aided by a grant from the Samuel S. Fels Fund.

cerebral blood flow have been frustrated hitherto by anatomic difficulties (abundant and inaccessible communications between the intracranial and extracranial parts of the cephalic circulation, particularly in the dog and cat) as well as by shortcomings in the various methods that have been used for this purpose (stromuhr, venturimeter, diversion of venous outflow into a calibrated vessel, thermocouple in brain tissue or in a vein effluent from the brain, thermostromuhr, rotameter). In the present experiments both of these objections have been met, the anatomic by the use of an animal (*Macacus rhesus*) in which blood carried by the internal carotids is distributed only to the brain and is the sole supply of that organ if the basilar artery is tied, the instrumental by timing the transit, through a glass tube of known volume, of an air bubble injected into the stream of blood carried from the common to the internal carotid arteries, the animal being narcotized with nembutal and heparinized and its basilar artery ligated.

In 14 experiments cerebral blood flow thus measured at the start of the experiment ranged from 0.38 to 0.81 and averaged 0.62 cc. per gram of brain per minute. Flow was consistently increased by intracarotid injections of non-depressor doses of histamine, nitroglycerin, theophylline and caffeine, as well as by inhalation of CO₂ (10%) in oxygen or of pure nitrogen; the effect of histamine was much greater and that of CO₂ much smaller than was expected from results of experiments on cats. Small doses of adrenalin and benzedrine intra-arterially consistently caused a significant decrease in cerebral blood flow sufficient in some instances to cause symptoms of cerebral anemia; with intravenous injections an increase in flow preceded the decrease and the latter was less striking though usually present. Ergotamine diminished cerebral flow consistently, but it also lowered blood pressure. Stimulation of the cervical sympathetic nerve did not decrease the flow in any of 9 attempts on 4 animals though typical ocular effects were observed. Metrazol, in convulsant doses, caused a pure increase in the flow. With insulin, blood pressure fell as hypoglycemia developed and then recovered; cerebral flow followed this, apparently quite passively. Further experiments are being made.

The Circulation in Traumatic Shock. MILTON L. CULLEN, A. E. SCHECTER, NORMAN E. FREEMAN, and M. K. LAWS (Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania). Shock was produced by trauma to the muscles of both thighs in 9 of 11 intact dogs and in 5 partially sympathectomized dogs. Local fluid loss was excessive in all instances. The earliest sign of shock was a marked reduction of peripheral blood flow as measured in the dog's uninjured paw. Hemoconcentration was not a significant finding. Shock was produced in 14 of 16 dogs by muscle trauma combined with fractures of two ipsilateral extremities but the local fluid loss was restricted by binding the extremities with tape. The amount of fluid lost into the injured extremities was measured. The earliest sign of shock was a marked reduction of peripheral blood flow. There was considerable hemoconcentration in comparison to the earlier experiments.

Blood volume determinations by the carbon monoxide method showed a substantial reduction of blood volume after trauma, and this reduction was only partially accounted for by local fluid loss.

Postmortem examinations suggest that at least part of the "lost" blood volume is to be found in the lumen and wall of the intestinal tract.

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ORIGINAL ARTICLES.

THE EFFECT OF AGE ON THE SUSCEPTIBILITY OF THE
ERYTHROCYTE TO HYPOTONIC SALT SOLUTIONS.

RADIOACTIVE IRON AS A MEANS OF TAGGING THE RED BLOOD CELL.*

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THE difference in susceptibility of red blood cells to hemolysis by hypotonic salt solution has been ascribed to a number of factors, among which are variations in osmotic resistance, varying degrees of permeability of the erythrocyte membrane, brought about by various causes including difference in the age of the red cells. At present it seems well established that the shape of the cell, or more explicitly the ratio between the thickness and the diameter, is the most important factor.^{3,6,9,19}

Convincing data regarding the rôle played by age of the erythrocyte as regards hemolytic susceptibility are not found in the literature of this subject. Some investigators find the morphologically immature red cells (reticulocytes, granulated red cell forms) more resistant to hypotonic salt solutions than the adult erythrocytes.^{1,14,20,21,23,24} Others find a decrease in the susceptibility of the same cell forms.^{4,5,8} Still others find no difference between the

* We are indebted to members of the Radiation Laboratory of the University of California and in particular to Drs. E. O. Lawrence and M. D. Kamen for the radioactive iron used in these experiments.

† On Official Commission from the Institute Oswaldo Cruz, Rio de Janeiro, Brazil.

immature and the adult forms.^{16-18,22} Buckmann and MacNaugher found that the young cells were less resistant in pernicious anemia and more resistant in anemia after hemorrhage.² Daland and Zetzel⁷ concluded that the age of the erythrocyte does not necessarily determine its behavior in hypotonic salt solution. They found the young cells (reticulocytes) more, less, or equally resistant than the adult cells in different diseases and even in the same patient with pernicious anemia in different regeneration periods following liver therapy. All such studies must necessarily be limited to the determination of different susceptibilities between reticulated or granular forms and the general run of the erythrocytes in the circulation, since no other means were available to determine the age of the cells than by histologic methods.

When the radioactive isotope of iron is administered to an anemic animal, some of it is very promptly used to form hemoglobin in the red blood cells.¹³ This iron when bound in hemoglobin within the cell does not undergo exchange with the other iron of the body,¹² and so affords a means of identifying the new cells as distinguished from those red cells which were present before and made up the bulk of the circulating cells. If a comparatively small amount of the iron is given as a single dose to an animal, the age of the red cells into which it is incorporated can be estimated to within a few days.¹³ This enables one to distinguish between cells of known ages ranging from a few days to several months and the general run of the cells in the circulation.

Methods. To determine the resistance of the erythrocyte, amounts of whole blood were added to salt solutions of varying concentrations, the proportions being the same for any one experiment and usually being in a ratio of 1:5. The actual amount of whole blood used depended upon the concentration of activity.

In a typical experiment 15 ml. of freshly drawn whole blood were added to each of a series of tubes containing 75 ml. of, respectively, 0.50, 0.45, 0.40, 0.35, 0.30% NaCl solutions and one tube with distilled water. After contact of about 20 minutes, the suspensions were centrifuged. The supernatant solutions were separated from the cells by suction. Aliquots of the supernatant solution were diluted with distilled water to permit reading in a Klett photoelectric colorimeter. These values, when related to the reading of completely hemolyzed cells (distilled water), represented the percentage hemolysis for each concentration of salt.

The supernatant solutions were separately ashed,^{10,11} the iron precipitated and a determination of the radioactivity made.¹² The activity was expressed as a fraction of that obtained from the supernatant of the cells treated with distilled water. Since only the radioactive cells contributed to this value, it is a measure of the hemolysis of the cells of known age due to labelling with the isotope.

Experimental Observations. In the preliminary experiments, anemic, iron-depleted dogs were employed. In these animals, due to the often repeated removal of large quantities of blood, the mean age of the red cells in the circulation is probably a matter of a few weeks, this depending on the frequency with which all the circulat-

ing cells are completely replaced by erythropoiesis. Therefore, the differences in age of the new tagged cells and general run of the red cells could be considerable only in the first few days of the experiments. Later normal animals were used, being subjected to two bleedings equivalent to about two-fifths of their blood volumes in order to stimulate hemoglobin formation shortly before the injection of the iron containing the radioactive isotope.

In Experiment 1, Dog 39-226, an adult, female mongrel setter weighing 10 kg., was depleted of iron reserves by repeated bleeding and the anemia was maintained in this way for 5 weeks' time. A series of 5 injections of ferric ammonium citrate containing the isotope were given. These were administered on successive days and consisted of 55 mg. of iron each. Seven days after the first and 3 days after the last injection, blood was withdrawn for determination of susceptibility toward salt solutions of various concentrations and the corresponding radioactivity of the remaining red cells and supernatant layers was measured. The animal was not disturbed for 9 weeks after which measurements were repeated (Chart 1).

Experiment 2 concerns Dog 38-137, an adult, female beagle, weighing 10 kg., which likewise had its iron reserves exhausted by an anemia of 6 weeks' duration. This animal was given a single injection of the radioactive iron by vein consisting of 71 mg. of the element in the form of ferric ammonium citrate. At this time, the blood hemoglobin level was 6 gm. per 100 ml. Three days later, blood was withdrawn for determination of hemolytic susceptibility and radioactivity. Unfortunately, the activity of the cells as measured was exceedingly low and as the results are not very good from a quantitative standpoint, they are not included. Under these conditions, it would be necessary to employ larger quantities of blood to establish the various points with precision. The same animal was allowed to continue for a considerable period subsequently in one of a series of experiments involving the determination of the life cycle of the red cell. At the end of 124 days, a single blood sample was taken and the hemolysis of the cells in saline studied (Table 1).

TABLE 1.—SUSCEPTIBILITY OF 4-MONTH-OLD CELLS.

Dog 38-137.

Age of tagged cells, days,	Conc. hypotonic sol., per cent.	Hemolysis of all cells (colorimetric), per cent.	Hemolysis of tagged cells (radioactivity) per cent.
124	0.41	63	44
130	0.36	92	82
130	0.39	66	45
130	0.42	34	29

Six days later, three equal aliquots of blood were treated with salt solutions of concentrations of 0.36, 0.39, and 0.42% and the hemolysis of the tagged cells and of the total cells determined.

Experiments 3 and 4 were conducted on animals which previous to the experimental work had been normal stock dogs. Dog 40-115,

an adult mongrel, weighing 16.7 kg., was bled about 200 ml. on each of 2 successive days. Immediately following the second bleeding, 125 mg. of iron as ferric ammonium citrate was injected by vein. Four days later, blood was withdrawn for determination of susceptibility to salt solutions and measurement of radioactivity. As can

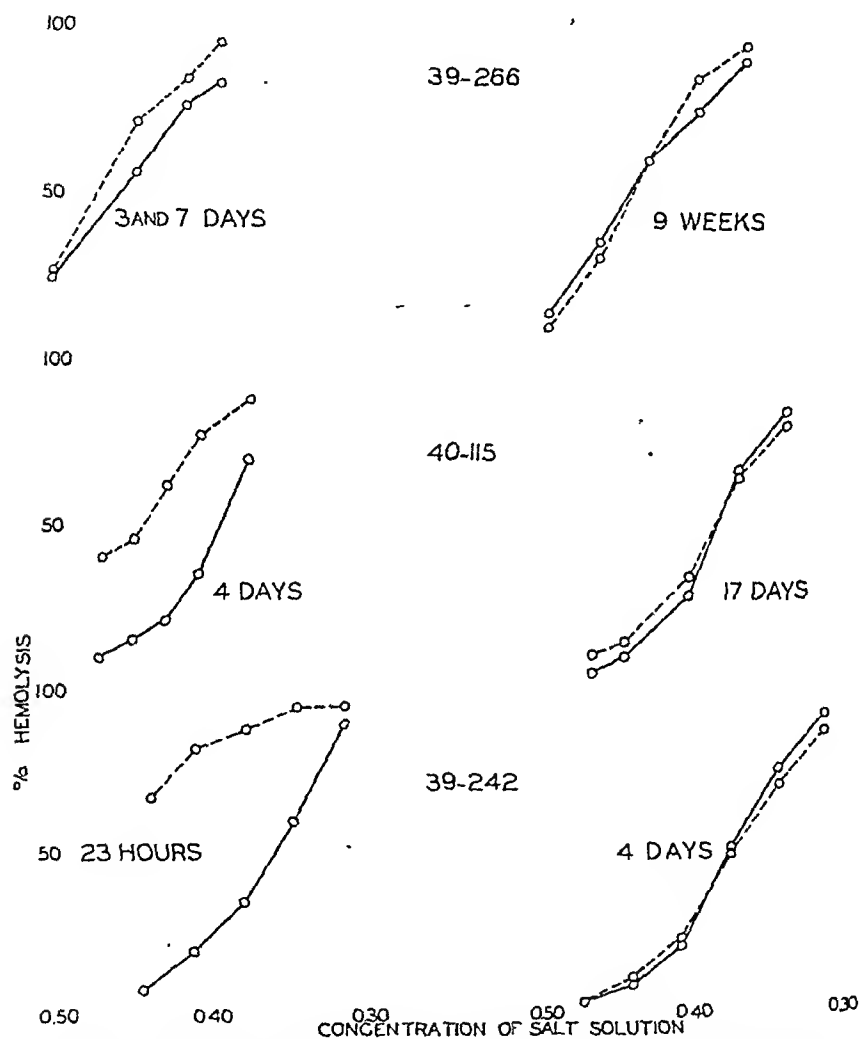


CHART 1.—Susceptibility at various known ages. o—o, hemolysis of all cells (colorimetry); o - - - o, hemolysis of labelled cells (radioactivity).

be seen in Chart 1, the curves for hemolysis of the cells in general, and the hemolysis of the tagged cells as measured by the radioactivity of the supernatant solutions, are widely divergent. Seventeen days after the injection of iron, blood was again drawn for these determinations and the curves are nearly identical.

Dog 39-242, a normal, adult mongrel, weighing 11.7 kg., was bled 250 ml. on each of 2 days and immediately after the latter bleeding was given an injection of 31 mg. of iron containing the isotope as ferric ammonium citrate by vein. In order to see if the divergence of the curves for total hemolysis and the radioactivity of the supernatant solutions would be more marked than in the 4-day experiment above, blood was taken for measurements after only 23 hours had elapsed. In Chart 1, the marked dissimilarity of the two curves can be seen. Four days after the injection, another sample of blood

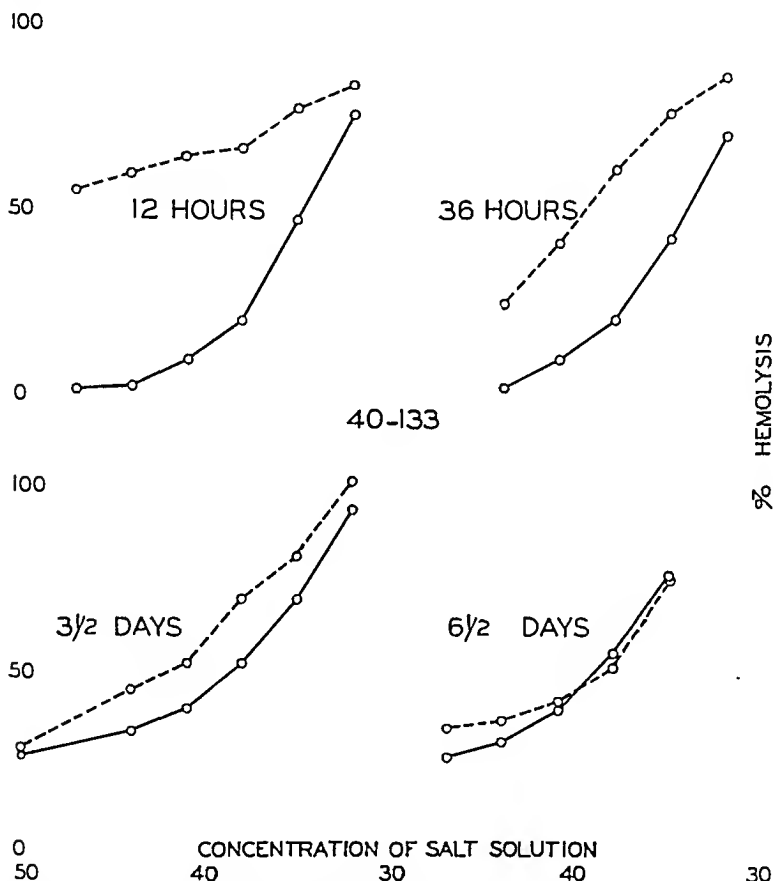


CHART 2.—Susceptibility decreases with age o———o, hemolysis of all cells (colorimetry); o — — — o, hemolysis of labelled cells (radioactivity).

was withdrawn for measurement, and it was found that the two curves were superimposed. It was therefore suggested that sometime approximating 4 or 5 days following injection was a crucial one as regards susceptibility differences.

Experiment 4 was carried out in an attempt to obtain a series of these curves in the same animal at different intervals during which the curves would be unlike. Dog 40-133, an adult, normal beagle, weighing 8.1 kg., was bled twice as the animals above and, 5 hours after the second bleeding of 200 ml., a single dose of 31 mg. of radio-

active iron was given by vein. Twelve hours after the injection, blood was withdrawn for study. Another bleeding was carried out at 36 hours, a third at 84 hours, and one at $6\frac{1}{2}$ days. The progressive approach of the curve for hemolysis of the tagged cells toward that for the whole mass of circulating cells can be seen in Chart 2.

Discussion. When the dogs employed for these studies have been anemic for long periods due to chronic hemorrhage, the mean age of the cells in the circulation will probably only be about several weeks. The exact age of the mean will be dependent upon the rate of replacement of the circulating cells by regeneration, and this in turn will be related to the diet and iron intake. Where normal dogs are employed, the average of the circulating red cells would be approximately one-half of the life span of the red cell, or probably over 60 days.¹⁵

It has been shown in a previous publication¹³ that when a single dose of iron containing the radioactive isotope is fed an anemic dog, the concentration of the radioactive hemoglobin in the circulation increases progressively for from 3 to 7 days. Therefore, it cannot be concluded that cells are 5 days old merely because this amount of time has elapsed since injection of the isotope. Rather, the mean age of the cells would be more likely to approach the order of 3 days, 7 days after administration.

Since red cells were actively being formed with the utilization of the radio-iron at a time interval of 4 or 5 days, and since the difference in hypotonic susceptibility between new-formed cells and older ones became negligible 5 or 6 days after administration of radio-iron, it would seem that only the very young red cells (less than 4 days of age) were less resistant to saline.

It seems worth noting that the resistance of the very old tagged cells (130 days of age) of Dog 38-137 was possibly a little greater than the other cells of the circulation. The latter would probably differ in age from the tagged cells by only a matter of several weeks, since when the isotope was administered this animal was iron depleted and anemic. Therefore, a gradually decreasing susceptibility toward the end of the life span of the red cell might not be seen in such marked contrast here as in the other experiments where the age of the cells differed more widely.

When more active iron becomes available, or measurement sensitivity is increased, it may become possible to extend these studies considerably. At present, it is possible only to study a small portion of the hemolysis curves in a single experiment because of the necessity of using large amounts of blood in order to obtain accurate activity measurements.

Summary. When radioactive iron is administered in a single dose to a dog in which there is a stimulus for hemoglobin formation, the isotope is promptly incorporated into the pigment in the red cell. These cells (identified by their radioactivity) can be regarded as

of known age and then be compared with those of the general run of the cells of the circulation as concerns susceptibility to hypotonic saline.

The very new cells in the circulation are found to be markedly less resistant to the hypotonic salt solution than are the other older cells. This difference in susceptibility disappears after a period of about 3 or 4 days.

There is an indication that possibly the very old red cells (130 days) are more resistant to hypotonic saline than the circulating cells of the mean age group.

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ERYTHROCYTE FRAGILITY CHANGES PRODUCED BY SULFANILAMIDE.

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SPLENIC enlargement after the administration of sulfanilamide has been previously described.^{3,5-7} In an earlier communication concerning the pathology of the spleen⁶ it was stated by one of us (W. A.): "The histologic appearance of the spleen was very suggestive of active hyperemia. Because of this it was proposed to test the fragility of the red blood cells to see if there was any deviation from the normal, and also to search for any other detectable

modification of the red blood cells." Since active splenic hyperemia is characteristic of hemolytic anemias, the fragility of the erythrocyte was stressed in the present study.

Method. The resistance of red blood cells to hemolysis by hypotonic saline solution was determined weekly in 15 rats receiving 1 gm./kg. sulfanilamide daily by stomach tube and in 5 control rats. These fragility tests were made using blood obtained by cutting the tail tip. Tubes were set up containing saline solution increasing in steps of 0.02% from 0.28 to 0.50% concentration. The readings were made after 1 hour at room temperature and again after 18 hours' incubation at 37°C. The highest saline concentration at which hemolysis was discernible was recorded in this investigation.

At the end of the second week, 2 untreated control and 3 sulfanilamide animals were sacrificed by decapitation and thereafter 1 control and 4 sulfanilamide animals were killed at approximately weekly intervals for a period of another month. The erythrocyte, leukocyte, reticulocyte and differential white blood cells counts were performed and hemoglobin (Sahli) content was determined. The spleens were removed and weighed. Routine gross and microscopic examinations were made on all organs.

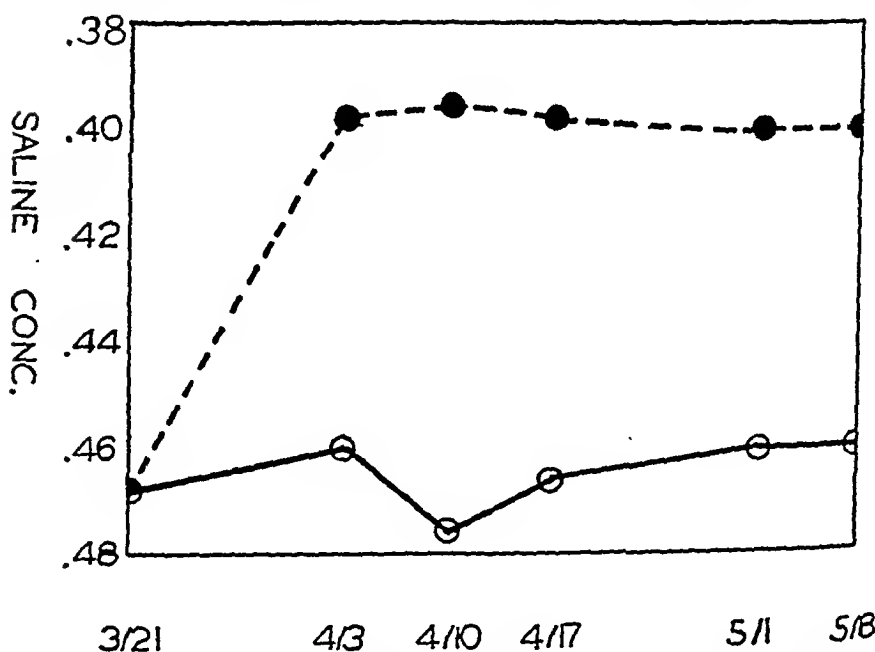


CHART 1.—Fragility changes after sulfanilamide administration. (●) Sulfanilamide treated rats. (○) Control (untreated) rats. Ordinate—saline concentration. Abscissa—date of fragility determination.

The average saline concentration for beginning hemolysis is shown in Chart 1. It was found that the resistance of the red blood cells to beginning hemolysis of the control rats remained essentially constant, initial hemolysis occurring in 0.46 to 0.48% saline. After 2 weeks of sulfanilamide administration (this being the first time

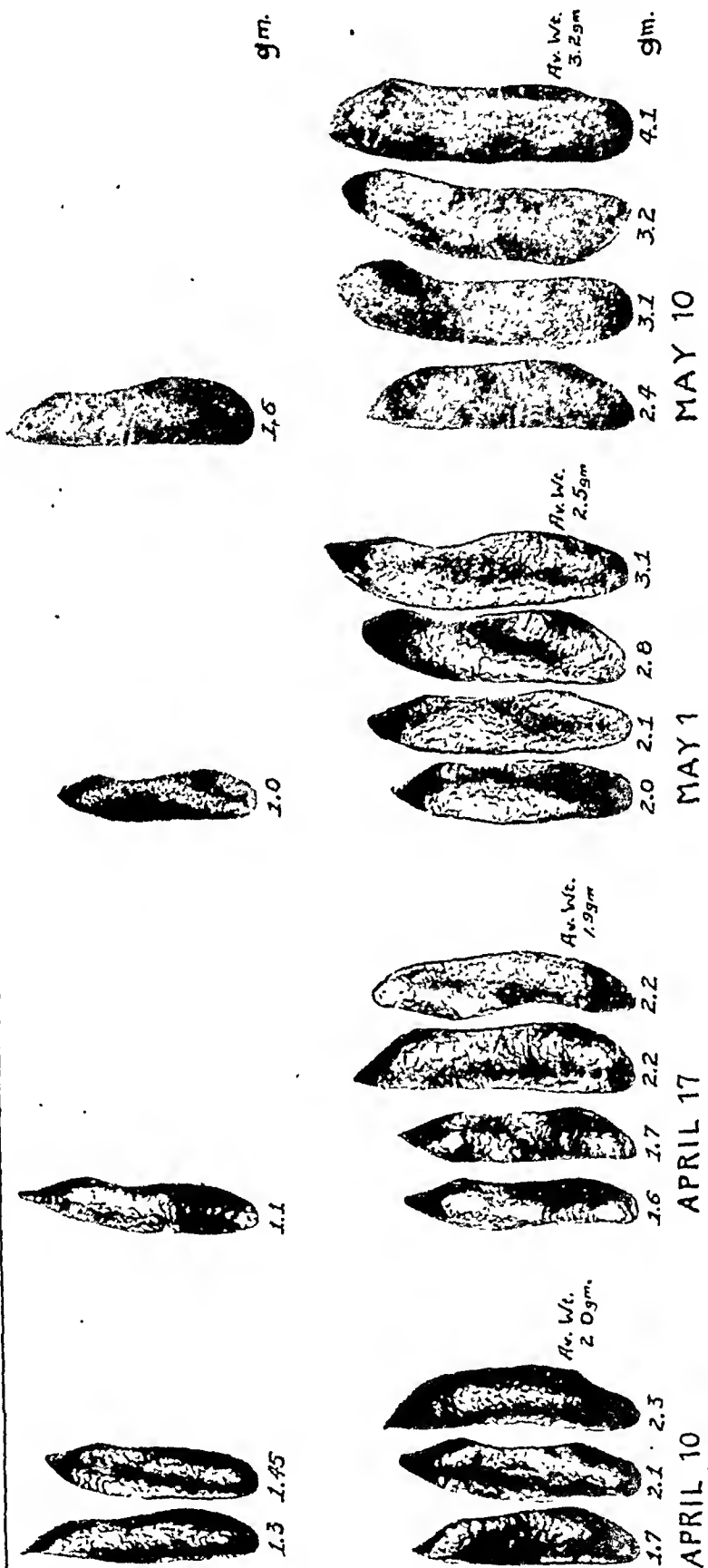


Fig. 1.—Splenomegaly in sulfanilamide rats. Upper row, control spleens; lower row, spleens from rats fed with sulfanilamide.

it was determined after instituting sulfanilamide), hemolysis of the red cells began at about 0.40. (In another series of rats, this change was already found to occur 18 hours after the first intraperitoneal injection of 2 gm./kg.) This value remained constant throughout the remainder of the experiment. The hemoglobin, erythrocyte, leukocyte and reticulocyte findings are in accord with those of Machella and Higgins.⁵ The control animals showed an average of 7,900,000 erythrocytes per c.mm. as the final readings. The treated rats, on the other hand, developed a progressive anemia with a final average count of 3,900,000 erythrocytes per c.mm. The average final leukocyte count in the former group was 9600 per c.mm., and in the treated rats 11,800. The average normal reticulocyte counts were 1.35 per 1000 erythrocytes as compared with an average of 7.5 in the treated rats.

The control spleens varied in weight from 1.0 to 1.6 gm. (average 1.29 gm.). The splenic weights of 7 sulfanilamide-treated animals in the first 4 weeks of the experiment varied from 1.6 to 2.3 (average 1.94 gm.). The 4 spleens in the 6th week varied from 2.0 to 3.1 (average 2.5 gm.), and in the final week they varied from 2.4 to 4.1 (average of 3.2 gm.) (Fig. 1). The enlarged spleens were firm and showed a deep purple or even black color. Microscopic examination showed an active hyperemia such as seen in hemolytic anemia, and, in addition, an exaggerated hemosiderosis which was most pronounced in the perifollicular region, so that an iron stain of the section revealed a blue ring completely encircling each follicle. The livers were often enlarged. Frequently there was considerable loss of hair leaving extensive areas of alopecia.

The findings of changes in fragility of the red blood cells would be in accord with the increased urinary porphyrins in rats^{9,10} and humans,⁹ the increased urobilinogen excretions in humans,² and the anemia^{1,3,5,8,10} and reticulocytosis⁵ which has been reported after sulfanilamide.

The fact that the red blood cells showed an increased resistance to hemolysis by hypotonic saline solution is still in accord with the concept that the pathologic state of the erythrocyte is the primary factor in hemolytic anemia, and that the spleen plays a secondary rôle. (For literature, see Klemperer.⁴)

Summary. The administration of sulfanilamide to rats results in an increased resistance of the red blood cells to hemolysis in hypotonic saline solution, and in splenomegaly with the histologic picture of active hyperemia such as seen in hemolytic anemia.

Since completing this manuscript Richardson (*J. Pharm. and Exp. Ther.*, 70, 370, 1940) reported the fragility changes in 3 mice fed 2% sulphanilamide for 2 weeks. He found that the blood in the sulphanilamide treated rats showed greater hemolysis in saline concentrations to 0.39%, but beyond this point the erythrocytes were more resistant.

We wish to express our appreciation to Miss Sally Woodford for her excellent technical assistance.

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PERNICIOUS ANEMIA COMPLICATED BY MYELOGENOUS LEUKEMIA.

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THE term leukanemia has long been used to describe an ill-defined syndrome of macrocytic anemia and leukemia, and even today appears at times as a special heading in the Quarterly Cumulative Index. In view of the recent advances in our knowledge of pernicious anemia as a deficiency disease, it seemed of interest to reëxamine the cases of leukanemia in the literature, and to report a case of myelogenous leukemia complicating well-established pernicious anemia.

Since 1900, when Leube⁸ first described what he felt was a new disease entity, numerous cases of so-called leukanemia have been reported, chiefly in the German literature. Sinek and Kohn¹⁵ reviewed the reported cases up until 1930 and rejected all of them except the one described by von Reichel.¹² In reëxamining the latter's report, however, the diagnosis of pernicious anemia is not conclusive. Likewise the cases of Elman and Marshall⁵ and Barns and Rosenheim¹ fail to fulfill the requirements of a combined diagnosis. Most authors (Naegeli¹¹ and Muller and Werthemann⁹) do not agree with Jacobsohn⁷ that the concept of leukanemia warrants a definite disease entity.

Well-substantiated cases of coëxisting chronic leukemia and an erythrocyte maturation factor deficiency anemia have been described by Rich and Schiff,¹³ Touw and Graafland¹⁵ and Doan.⁴ To these we wish to add the following case report in which the

diagnosis of true Addisonian anemia terminating in myelogenous leukemia is justified.

Case Report. E. A. (No. 54059), a 57-year-old white married housewife, entered the Cincinnati General Hospital on March 28, 1936. She had been in perfect health until the fall of 1935 when she noted the onset of anorexia, weakness, and dyspnea. This became progressively worse until February, 1936, when it was exaggerated by nausea and vomiting.

Physical examination revealed a well-developed and obese woman despite evidence of considerable weight loss. The skin and mucous membranes were very pale. She had gray hair, blue eyes with an icteric tint to the sclerae, and several flame-shaped fresh retinal hemorrhages. The tongue was atrophic and there was moderate dependent edema. The liver, spleen and lymph nodes were not palpable. The neurologic examination was negative. The remainder of the physical examination disclosed no abnormalities.

The laboratory studies, disclosing a severe macrocytic anemia with leukopenia and the characteristic response to liver extract, are shown in Chart 1. The gastric analysis showed achlorhydria and a low total acid content by the alcohol-histamine method. Clinical improvement as well as hematologic response was noted.

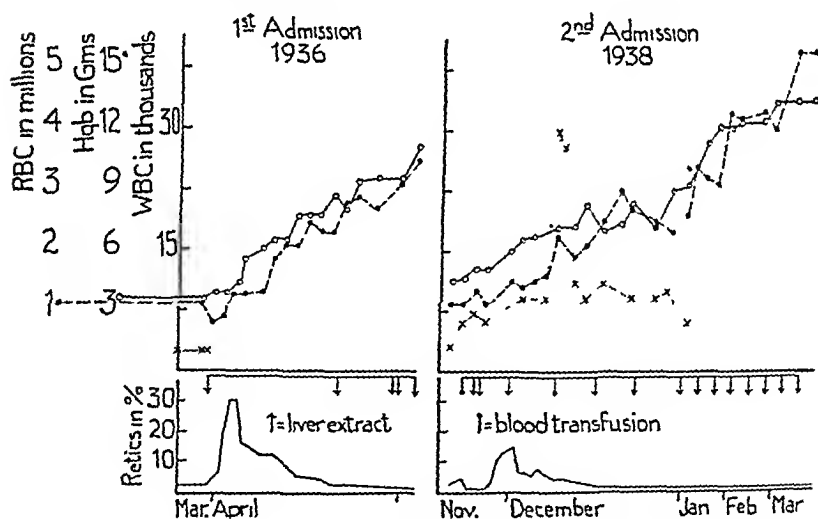


CHART 1.—Hematologic data of case reported.

After an interval of 2½ years, she reappeared at this hospital on Nov. 21, 1938, because of a relapse in her anemia, associated with cessation of specific treatment and the development of symptoms referable to the central and peripheral nervous systems.

The physical findings now were similar to those of the first admission plus the evidences of peripheral neuritis and dorso-lateral sclerosis of the spinal cord. The laboratory findings are seen in the second part of Chart 1. Sternal puncture revealed a megaloblastic bone marrow of the type characteristic of pernicious anemia. On this admission she was given a trial with an antianemic substance of undetermined potency, but on the fifth day, because of the appearance of a severe urinary tract infection, this was stopped and transfusions and potent liver extract given. By the middle of April, 1939, the blood picture was normal and great improvement was noted in her clinical condition.

Her third admission to this hospital was on Feb. 8, 1940, because of hemoptysis of 8 days' duration. Since April, 1939, she had substituted oral capsules for intramuscular liver. The physical examination revealed no cause for the hemoptysis. Roentgen rays of the chest were interpreted as indicating chronic bronchitis and bronchiectasis. The hematologic findings disclosed that the erythrocytes were 2.9 million, the hemoglobin 11 gm., the hematocrit 30, and the mean corpuscular volume 103. The leukocytes were 18,700 with neutrophils 75%, lymphocytes 21%, monocytes 3%, eosinophils 1%. It was noted that one-third of the neutrophils were "young forms." The platelet count was 406,000, the bleeding time 3 minutes, and the clotting time 2 minutes. She remained in the hospital 5 days and no hemoptysis occurred.

The fourth and final admission occurred on Sept. 18, 1940, 4½ years after her first admission, when she entered the hospital in coma and died 45 minutes later. In the 7 months' interval between her last two admissions she was fairly well. She did her own housework, but was limited in it by weakness and dyspnea, which was not improved by liver injections or later by oral capsules given by her private physician. On Sept. 15, 1940, she suddenly developed diarrhea which continued for 3 days until she lapsed into coma 6 hours before arrival at the hospital.

When admitted to the hospital she was in deep coma. The temperature was 101°, the pulse undeterminable, the respirations 40. The abdomen was distended and the liver and spleen were not palpable. Emergency stimulants were administered in vain. Postmortem blood studies (heart's blood) showed the erythrocytes to be 2.6 million, hemoglobin 11.8 gm., leukocytes 100,000 with the following differential: myeloblasts, 3%; myelocytes A, 2%; myelocytes B, 16%; myelocytes C, 31%; metamyelocytes, 5%; stab forms, 16%; neutrophils, 18%; lymphocytes, 2%; basophils, 3%; and basophilic myelocytes, 1%.

Autopsy (5 hours postmortem, by Dr. H. Shanes): The *spleen* was markedly enlarged (1075 gm.), soft, friable, and a deep purplish-red with a definite grayish cast. The Malpighian corpuscles were not prominent. The *liver* was also markedly enlarged (1085 gm.). It was soft, friable, and with no gross evidence of necrosis or infiltration. The *lymph nodes* were grossly normal. Sections of the *bone marrow* taken from the body of the sternum, ribs, and lumbar vertebræ were all similar grossly, and presented a porous sponge-like appearance, with a homogeneous dull grayish-yellow color.

Microscopically, there was evidence of chronic myeloid leukemia with infiltration of the leukemic cells into the spleen, liver, lung, uterus, and submucosal layer of the stomach. Giemsa stains of several sections of bone marrow revealed young cells of the myeloid series completely filling the marrow. Of some interest was the absence of pronounced leukemic infiltration in the lymph nodes and kidney. There was also evidence of posterior (and suggestive lateral) column demyelination of the spinal cord. In addition, there was demonstrated acute ulcerative typhlitis and chronic active pyelonephritis.

Discussion. We think that there is little doubt that this case represents pernicious anemia complicated by subacute myelogenous leukemia. There may be many sources of error in attempting to make a combined diagnosis. Numerous authors (Sturgis and Isaacs,¹⁷ Castle and Minot,³ Sharp *et al.*¹⁴ and Heek,⁶) have shown that in cases of pernicious anemia in relapse, especially when the red count is low, a small number of myelocytes, and even an occasional myeloblast, may appear in the peripheral blood, and that

during remission a left shift in the neutrophils occurs with the occasional appearance of a few younger forms in this series. We likewise have noted in our own cases of pernicious anemia similar abnormalities. A bone marrow examination and the subsequent course of the patient after therapy, with a rise in the red count and a disappearance of the neutropenia, is sufficient evidence to indicate a so-called myeloid reaction in pernicious anemia. A persistent neutropenia despite adequate treatment should raise the question of a subleukemic leukemia.

Just as pernicious anemia may for a time simulate leukemia hematologically, so may leukemia simulate pernicious anemia. It is well known that while the associated myelophthisic anemia is most often normocytic, it may frequently be macrocytic. This, plus the usual leukopenia (in subleukemic states) and the thrombocytopenia, may suggest pernicious anemia. If the differential leukocyte count is carefully examined, pathologic cells will almost always be found in cases of leukemia, and more particularly bone marrow biopsy should reveal definite evidence of leukemia.

One can only speculate concerning these two diseases in the same patient, for although the most reasonable explanation is that of coincidence, it might be supposed that improperly treated pernicious anemia eventually predisposes the marrow to leukemic changes. The extreme rarity of this combination, despite the frequency of inadequately treated pernicious anemia, makes this most unlikely. Murphy,¹⁰ who has seen a great number of cases of pernicious anemia, does not even mention the possibility of leukemia in his discussion of the complications of the disease. A third, but for similar reasons equally tenuous hypothesis, is that there is a fundamental defect, possibly hereditary, of the blood-forming organs, which makes the individual susceptible to either or both diseases. Along this line there are several reports in the literature describing leukemia and pernicious anemia or a pernicious anemia-like disease in siblings (Strandell,¹⁶ and Bichel²). Until further evidence is available concerning the fundamental defect in leukemia, one must fall back upon chance as the most likely explanation of its association with pernicious anemia.

Summary and Conclusions. 1. The cases of leukanemia in the literature are reviewed and most of them rejected as failing to fulfill the requisites for the diagnosis of both pernicious anemia and leukemia.

2. The authors' own case is reported as a true Addisonian anemia terminating in myelogenous leukemia.

3. Pernicious anemia and subleukemic leukemia may for a time simulate each other. The difficulties in making a combined diagnosis are discussed.

4. The most satisfactory explanation for the occurrence of these two diseases in the same patient is that of coincidence.

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HEMATOLOGIC CHANGES FOLLOWING SPLENECTOMY IN
MAN, WITH PARTICULAR REFERENCE TO TARGET
CELLS, HEMOLYTIC INDEX AND LYSOLECITHIN.*

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THE dramatic results which often attend splenectomy in cases of hemolytic anemia and thrombocytopenic purpura have led us to detailed study of the splenectomized individual as a means of attaining knowledge of splenic function. The present publication deals with the study of 19 individuals who were splenectomized for various conditions and who were carefully studied at various intervals. In particular, modern hematologic methods were utilized with especial reference to "target" cells, hypotonic fragility, blood platelets, the question of blood destruction, and the "lysolecithin" metabolism. From these studies evidence was obtained in support of the concept that one or more splenic hormones exist, as well as confirmation of the frequently expressed view that the spleen aids in blood destruction.

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Material. Investigations were performed in 8 normal individuals and in 19 patients splenectomized for various causes from 4 weeks to 15 years previous to our studies. The splenectomized material may be divided into two groups: (1) *non-hemolytic*, 11 cases; traumatic rupture, 2; "Banti's" disease, 1; Gaucher's disease, 1; lymphatic leukemia, 1; and idiopathic thrombocytopenic purpura, 6. (2) *hemolytic*, congenital type, 4; acquired type, 4. This grouping was thought advisable because the cases with increased hemolysis showed marked changes in the shape of erythrocytes as well as greatly increased blood destruction preoperatively, differentiating them sharply from the non-hemolytic group.

Methods. A. HEMATOLOGIC METHODS. *Hemoglobin:* Evelyn or Cenco photoelectric method (100% = 15.5 gm. per 100 cc. of blood).

Red cell count; white cell count: U. S. Bureau of Standards certified pipettes and hemocytometers used; automatic shaker.

Platelet count: Method of Dameshek.^{3a} Normal count, 400,000 to 900,000 per c.mm.

Reticulocyte count: Both "dry" and "wet" methods used. In the "wet" method, the technique of Dameshek^{3a} was used.

Hematocrit: Venous blood collected in 5-cc. vials ammonium oxalate 6 mg., and potassium oxalate 4 mg. in Wintrobe type hematocrit tubes for 25 minutes at 3500 r.p.m.

Mean corpuscular volume: Normal range 84 to 94 cu. micra.

Mean corpuscular diameter: Price-Jones curves obtained by counting diameters of 200 cells using calibrated micrometer eye-piece. Normal mean diameter 7.4 to 7.6 micra.

Mean corpuscular thickness: $\pi \left(\frac{\text{M.C.V.}}{\text{Diameter}} \right)^2$. Normal thickness 1.9 to 2.2 micra.

Howell-Jolly bodies: Expressed in per cent of 100 red blood cells from Wright's stained films. Normally none present.

Target cells: Expressed in per cent of 100 red blood cells from stained films, in which these cells have the appearance of a "bull's eye" or target. In fresh preparations of blood, they are thin and highly flexible, assuming cup and bowl shapes. Normally less than 1% are present.

Fragility of the red cells to hypotonic solutions of sodium chloride: Method of Daland and Worthley.⁸ Normal values: Hemolysis begins at 0.46% to 0.44%; complete at 0.26% to 0.24%.

Bone-marrow biopsy: Sternal puncture method used.

B. METHODS USED IN THE INTERPRETATION OF ERYTHROCYTE DESTRUCTION. *Bilirubin:* Qualitative methods of van den Bergh. Quantitative method of Malloy and Evelyn;²⁵ Evelyn or Cenco photoelectric colorimeter used. Normal 0.3 to 1 mg. per 100 cc.

Urobilinogen in feces: Quantitative determination. Method of Watson,^{33a} based on the original method of Terwen³² and the modification of Fuerth and Singer.¹¹ Normal level of urobilinogen excretion 40 to 200 mg. per day (average of 4-day collection of feces).

Hemolytic index: $\frac{\text{Urobilinogen output per day}}{\text{Total hemoglobin in gm.}} \times 100$. This index (first proposed by Belanogowa⁴) expresses the urobilinogen excretion per day in relationship to 100 gm. of hemoglobin. Normal value 11 to 21 mg. per 100 gm. of hemoglobin. The total hemoglobin is computed from the hemoglobin content in grams per 100 cc. of blood and from the total blood

volume. The advantage of the hemolytic index is that it takes into account the fluctuations which occur in urobilinogen output with variations in the total mass of hemoglobin in the body.

Blood volume: Method of Gibson and Evans,¹² using the Evans blue dye, and the Evelyn photoelectric colorimeter (micro attachment).

C. **LYSOLECITHIN.** *Determination of lysolecithin content of blood:* Method of Singer,^{31b} the hemolytic titer of a serum extract containing this lysin is determined.

Lysolecithin "quotient": The lysolecithin titer of unincubated serum is compared to that of an aliquot sample of incubated unmoved serum. Singer^{31c} has shown that the lysolecithin titer of normal serum (1:2 to 1:8 in man) is increased two to eight-fold by incubating the serum for several hours. This increase, which is apparently due to the action of an enzyme normally present in plasma is expressed in the lysolecithin quotient:

$$\frac{\text{Lysolecithin content of unincubated serum}}{\text{Lysolecithin content of incubated serum}} = \text{LLQ}$$

Normally this quotient in circulating blood is a fraction of 1, i. e., $\frac{1}{2}$ to $\frac{1}{8}$.

TABLE 1.—NORMAL CASES.

Case.	Sex.	Age.	Hb., gm.	Hb., %	Daily fecal urobilinogen, mg.	Hemolytic index.	Expected blood volumes, in cc.*			Determined blood volume, in cc.			Total circulating Hb., gm.	Lysolecithin content.		
							R.B.C.	Plasma.	Total.	R.B.C.	Plasma.	Total.		Unincubated.	Incubated.	Lysolecithin quotient.
1	M	32	15 0	97	66 2	11 1	1977	2193	4170	1914	2074	3988	598	1:2	1:8	1:4
2	F	40	14 7	95	75 0	11 2	1763	2337	4100	1994	2540	4534	667	1:8	1:16	1:2
3	M	25	15 6	100	85 6	11 4	2475	3025	5500	2280	2520	4800	749	1:4	1:32	1:8
4	M	63	14 6	94	86 5	12 3	2295	2805	5100	1966	2830	4796	700	1:4	1:16	1:4
5	F	64	13 9	90	68 0	13 3	1484	1966	3450	1222	1733	2955	511	1:4	1:8	1:2
6	M	25	17 2	111	180 0	19 2	2637	3223	5860	2660	2770	5430	934	1:2	1:8	1:4
7	F	38	13 3	86	92 1	20 3	1527	2023	3550	1275	2125	3400	452	1:4	1:16	1:4
8	M	.	13 2	85	105 5	20.8	2070	2530	4600	2051	2558	4609	508	1:4	1:16	1:4

* Expected blood volumes based on the surface areas of the patients.

Results (Tables 1 and 2). 1. *Hemoglobin:* Although in most instances there was a slight reduction in hemoglobin values, in only 4 of the 9 cases was there definite anemia (below 12.5 gm.—80%). These were Cases 1 (atypical leukemia), 3 (Gaucher's disease), 8 (hepatic cirrhosis) and 15 (continuing or relapsed hemolytic anemia).

2. *Red blood cell count:* Of the 19 splenectomized patients, 3 (Cases 8, 15, and 18) showed red cell counts below 4 million per c.mm. In these cases, particularly in Case 15, the anemia was in all probability caused by continuation of the underlying pathologic process. Thus there were no cases in which anemia clearly related to splenectomy *per se* was present.

3. *Leukocytes* (Table 3): The white cell count was definitely elevated (above 12,000) in one-half the cases and above 10,000 in 12 of 19. However, in Case 1, chronic lymphatic leukemia was present several years after splenectomy for "Banti's disease," and

TABLE 2.—SPLENECTOMIZED CASES.

Case		Diagnosis	Time after splenectomy.	Hb, gm	Hb, %	RBC, millions per c mm	WBC, thousands per c mm	Platelets, thousands per c mm	Reticulocytes, %.	Howell-Jolly bodies, %	Target cells, %	Hypotonic fragility, % NaCl solution		MCV, cu micra		MCD, "micra	MCT, "micra	Serum bilirubin, mg per 100 cc	Fecal urobilinogen, daily output, mg	Hemolytic index, mg per 100 gm of Hb	† Expected blood volumes, in cc			Determined blood volumes, in cc			Total circulating Hb, gm	Lysocellin content		Typhoid quotient		
												Begins	Complete	Group I	Group II Hexolytic						RBC	Plasma	Total	RBC	Plasma	Total		Unincubated	Incubated			
1	M 15	Lymphatic leukemia	8 yrs	12.0	77.5	17.8	663	1.1	0.3	20.0	10.08	83.3	7.0	1.81	0.38	17.6	3.0	1971	2109	1380	1761	2312	4123	195	1.1	1.4	1.1	1.1	1.1	1.1	1.1	
2	M 21	Traumatic rupture	9 mos	11.9	96	19.0	10.6	2055	0.8	0.1	9.6	10.08	88.1	7.3	2.31	0.68	55.0	8.0	2520	3080	5000	2556	2770	5326	764	1.2	1.8	1.1	1.1	1.1	1.1	1.1
3	M 10	Gaucher's disease	20 mos	10.3	66	12.18	932	2.0	0.3	2.1	11.16	85.1	8.0	1.09	0.37	29.1	11.0	636	1141	2080	695	1263	1958	202	1.1	1.4	1.1	1.1	1.1	1.1	1.1	
4	F 15	Purpura	18 mos	11.7	92	19.15	626	1.1	0.7	2.7	12.12	87.2	7.2	2.11	0.77	37.5	6.5	1711	2266	3950	1703	2258	3961	560	1.1	1.4	1.4	1.4	1.4	1.4	1.4	
5	F 20	Purpura	3 yrs	13.1	86	16.13	977	1.5	0.5	0.5	12.12	94.5	7.8	1.97	0.33	61.4	11.4	1733	2297	1030				510†								
6	F 18	Purpura	3 yrs	11.2	91	16.01	666	0.5	2.2	3.1	12.44	93.0	7.2	2.30	0.37	45.8	6.1	1570	2080	3050	2270	3020	5290	750	1.1	1.4	1.4	1.4	1.4	1.4	1.4	
7	F 18	Purpura	9 mos	11.7	95	19.15	1137	1.1	0.9	1.6	18.08	98.8	7.7	2.12	0.26	27.8	1.0†	1763	2337	4100				603†	1.2	1.2	1.1	1.1	1.1	1.1	1.1	
8	F 19	Cirrhosis of liver	13 mos	10.1	65	17.71	561	0.9	0.7	11.2	12.08	98.9	7.8	2.07	0.97	31.3	5.7	2305	3135	5500	2001	3413	5417	818	1.2	1.2	1.1	1.1	1.1	1.1	1.1	
9	M 10	Traumatic rupture	15 yrs	15.0	102	5.77	807	0.8	1.3	0.2	16.20	91.2	7.5	2.07	0.50	72.9	8.0	2412	2918	5360	2119	2728	5147	818	1.2	1.1	1.2	1.1	1.1	1.1	1.1	
10	M 15	Purpura	7 wks	13.0	94	18.10	510	1.0	0.8	2.7	12.48	87.7	7.3	2.09	0.32	22.2	3.4	2295	2805	5100	1961	3029	1990	619	1.1	1.8	1.8	1.8	1.8	1.8	1.8	
11	F 25	Purpura	1 wks	13.2	85	5.10	1015	2.2	0.1	2.1	12.40	84.2	7.6	1.86	0.30	25.2	5.0	1763	2337	4100	1442	1929	3371	115								
12	F 36	Acquired hemolytic anemia	1 yrs	11.0	90	13.12	661	0.8	1.3	1.3	16.12	107.2	8.1	2.08	0.21	30.0	5.2†	1763	2337	1100					1.1	1.1	1.1	1.1	1.1	1.1	1.1	
13	M 1	Acquired hemolytic anemia	3 yrs	13.0	91	13.91	521	1.6	0.3	2.1	12.16	90.4	7.1	2.28		16.0	5.8†	959	1171	2130				279†								
14	F 11	Acquired hemolytic anemia	1 yr	15.0	96	5.11	718	2.7	0.4	1.9	12.41	90.3	7.1	2.10	0.95	86.4	11.8	1733	2267	4030	1701	2160	3873	581	1.1	1.1	1.1	1.1	1.1	1.1	1.1	
15	F 12	Acquired hemolytic anemia	9 yrs	8.8	57	2.19	1215	25.2	0.6	0.3	12.20	103.1	7.6	2.27	1.35	105.0	119.0	1570	2050	3050	913	2840	3771	192	1.1	1.1	1.1	1.1	1.1	1.1	1.1	
16	M 11	Congenital hemolytic anemia	2 yrs	11.5	91	18.89	1091	1.1	0.5	0.2	56.12	90.0	6.3	2.88	0.88	53.3	7.5	2310	2960	5200	2231	3057	5288	767	1.1	1.1	1.1	1.1	1.1	1.1	1.1	
17	F 10	Congenital hemolytic anemia	2 yrs	13.9	90	1.71	1172	3.7	0.1	0.0	61.22	85.2	6.1	2.91	1.07	30.3	10.5†	868	1182	2680												
18	F 13	Congenital hemolytic anemia	8 yrs	13.2	85	3.8	159	0.3	0.1	0.5	60.20	100.5	7.1	2.51	0.97	69.7	11.0	1726	2291	1020	1152	2120	3772	108								
19	M 15	Congenital hemolytic anemia	7 mos	15.9	102	5.12	621	0.8	0.6	0.0	45.16	53.6	7.1	2.11	0.90	79.5	7.2	1710	2090	1800	1410	1910	3306	595	1.2	1.2	1.1	1.1	1.1	1.1	1.1	

MCV = mean corpuscular diameter MCT = mean corpuscular thickness
 MCD = mean corpuscular diameter MCT = mean corpuscular thickness
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in Case 15 there was persistent hemolytic anemia with secondary leukocytosis. That the leukocytosis was not a temporary phenomenon is attested by the fact that it was still present in several cases operated upon at least 3 years previously.

TABLE 3.—LEUKOCYTE AND DIFFERENTIAL COUNTS IN SPLENECTOMIZED CASES.

Case.	W.B.C. (thousands) per c.mm.).	N.	L.	M.	E.	B.
1	17.8	34	47	16	3	0
2	10.6	71	19	9	1	0
3	18.3	55	36	3	4	2
4	15.5	43	45	12	0	0
5	13.3	44	30	15	11	0
6	6.1	46	36	17	1	0
7	15.6	66	25	9	0	0
8	7.1	32	42	18	7	1
9	7.7	56	27	14	2	1
10	10.2	51	33	11	5	0
11	10.4	52	36	12	2	0
12	12.8	50	35	7	8	0
13	9.4	22	68	6	4	0
14	14.0	45	40	14	1	0
15	19.5	67	17	11	3	2
16	8.9	48	40	9	2	1
17	7.4	56	32	11	1	0
18	8.5	69	23	6	2	0
19	12.4	49	29	15	6	1

Despite the elevation in leukocyte count commonly present, the neutrophils usually showed a *relative* reduction in their number. Thus the percentage of neutrophils was less than 60 in 15 of the 19 cases. The absolute number of granulocytes was generally normal, although in several cases (Cases 6, 8, 9, 13, 17) an absolute reduction in granulocytes was present. Conversely, the lymphocytes and monocytes were generally increased in both a relative and absolute fashion. It is noteworthy that in 9 of the 19 cases, the monocyte percentage was 12% or over. Seven of the cases showed an eosinophilia of 4% or over.

4. *Platelets*: Eight of the 19 patients (Cases 2, 3, 5, 7, 11, 15, 16, 17) showed increased platelet counts (above 900,000 per c.mm.). The highest count (2,055,000) was observed in Case 2, operated upon 9 months previously because of traumatic rupture of the spleen. In 3 cases of thromboeytopenic purpura observed 4 weeks, 8 months and 2 years respectively after operation, the platelet counts were still abnormally high and the same finding was present in 2 cases of hemolytic anemia operated upon 2 years previously. There was no definite parallelism between elevations in the leukocyte and platelet counts, although some cases showed both.

5. *Reticulocytes*: The reticulocyte counts were generally within the normal range of 0.3% to 1%. In Case 3 (Gaucher's disease) the reticulocyte count was 2% and in Cases 14 and 17 (splenectomized for hemolytic jaundice) the reticulocytes numbered 2.7% and 3.7% respectively. Case 15, with severe hemolysis and spher-

cytosis persisting 9 years after splenectomy, had 25.2% reticulocytes. Thus no effect upon the reticulocyte level by splenectomy *per se* was discovered.

6. *Howell-Jolly bodies*: These definitely pathologic erythrocytes were found in varying number in *all* the cases regardless of the time elapsed since operation. This finding was the most constant one encountered in our studies.

7. *Target cells*: These recently described³ abnormal erythrocytes were present in increased numbers (above 1%) in 12 of the 19 cases (Cases 1 to 4, 6 to 8, 10 to 14). Although we have set an arbitrary level of 1% as the upper limit of normality, ordinarily very few target cells are found. All cases without persistent hemolytic anemia (with the exception of Cases 5 and 9) showed an increase of target cells. Of great interest were the contrasting findings after splenectomy between the cases of acquired and congenital hemolytic jaundice. In the congenital group (Cases 16 to 19) target cells were not increased, whereas in the acquired group, despite well-marked spherocytosis prior to splenectomy, target cells were definitely increased over normal. This finding was associated with a complete disappearance of the spherocytosis. There was no parallelism between the number of Howell-Jolly bodies and target cells. No nucleated red cells were found in the peripheral blood in our cases.

8. *Hypotonic fragility*: Haden¹⁴ demonstrated the relationship which exists between the thickness of the erythrocyte and its hypotonic fragility. The thicker the red cell, the more fragile it is in hypotonic salt solution and *vice versa*. Following splenectomy in Cases 1 to 14 (showing normal or diminished hemolysis) the hypotonic fragility of the erythrocytes was decreased in almost every instance. The decreased saline fragility was more clearly expressed in the so-called "minimum fragility," *i. e.*, that solution which showed complete hemolysis. Whereas normally, complete hemolysis occurs in solutions 0.30% to 0.24% NaCl, after splenectomy complete hemolysis took place only in solutions 0.16% to 0.08% NaCl. There was a direct parallelism between the increase in minimum resistance and that of the relatively thin target cells. In cases of hemolytic anemia (Cases 15 to 19) with persistent spherocytosis, the maximum fragility remained *increased*, although the minimum fragility might be diminished.

M.C.V., M.C.D., M.C.T.: The mean corpuscular volume was in general little affected, most cases showing normal values (between 84 and 94 cu. micra), although a few showed borderline macrocytosis. Except in the congenital hemolytic group, the mean cell diameter was either normal or slightly increased. Cases 3, 5, 8 and 12 presented values of 8.0, 7.8, 7.8, and 8.1 respectively. Of these, Cases 3 (Gaucher's disease) and 8 (hepatic cirrhosis) showed definite evidence of liver disease in which macrocytosis is not uncommonly present. Case 12, with both an elevation in the mean

cell volume and diameter was an example of cured acquired hemolytic anemia. The mean cell thickness was within normal range (1.7 to 2.3 micra) in all the cases except those of the congenital group, in which it was increased.

8A. *Bone-marrow findings:* The bone-marrow was studied in several cases but sufficiently detailed changes to warrant any statement of results have thus far not been found.

9. *Bilirubin:* The bilirubin values of most of the cases were within normal limits. The congenital hemolytic cases tended to show persistent slight bilirubinemia even after splenectomy.

10. *Urobilinogen excretion in the feces; Hemolytic index:* The daily urobilinogen excretion expressed in absolute values was either normal (40 to 200 mg. per day, Cases, 2, 4, 5, 6, 9, 14, 16, 18, 19), or less than normal (Cases 1, 3, 7, 8, 10 to 13, 17). That a low absolute daily value for urobilinogen does not always indicate a diminution in the output of the pigment may be recognized from the hemolytic index. This was determined in 14 of the 19 cases and was found to be lowered (less than 11 mg.) in 10, *i. e.*, in about two-thirds of the cases. Only in Cases 3, 14, and 18 was the index normal and in Case 15 (chronic hemolytic anemia) it was increased. The normal or slightly increased index in these cases was probably adequately explained by consideration of the various underlying pathologic processes. Of particular interest was the fact that 3 of 4 cases splenectomized for congenital hemolytic jaundice, although continuing to show slight spherocytosis and an increased saline fragility, nevertheless presented a low hemolytic index. No definite parallelism between the number of target cells present and the low hemolytic index could be demonstrated, nor was there any relationship of the index to the time after operation. Thus, a low index was present in Case 9, operated upon 15 years previously for traumatic rupture of the spleen.

11. *Blood volume:* Determination of the hemolytic index, which involves measurement of the blood volume, gave us the opportunity to compare the actual blood volume with the expected blood volume as computed from the surface area. Relatively small deviations from the expected volumes were found, except in Case 6 in which a definite increase in volume was noted and in Case 11 where the blood volume was definitely decreased.

12. *The lysolecithin metabolism:* One of us^{31b,c} has previously investigated the mechanism of the production of lysolecithin, a hemolytic substance which was discovered in normal blood serum by Bergenhem and Fåhræus.⁵ This mechanism can be expressed by the lysolecithin quotient. (L.L.Q.) Normally, in circulating blood (*i. e.*, blood in motion) this quotient is always a fraction of 1. In the reservoir blood of the spleen, which is at least temporarily excluded from the circulation and presumably acts like incubated unmoved blood, the LLQ was found to be 1. The spleen, which may be

termed the "incubator of the body," at least as regards lysolecithin and its action upon red blood cells, produces a material amount of lysolecithin which cannot be further increased by incubation.

Following splenectomy in 6 of 14 cases studied, the lysolecithin content of the unincubated serum from the peripheral blood was considerably lower than in normal individuals, a finding also obtained by Gripwall.¹³ Normally, complete hemolysis of normal red cells occurs in dilutions of 1:2 to 1:16 of lysolecithin extracted from 10 cc. of serum. In the 6 cases above mentioned, complete hemolysis was observed only in dilutions of 1:1. In 8 of 14 cases examined, no increase of the lysolecithin content of the serum occurred after incubation, resulting in a LLQ of 1. Since there was no question of "reservoir blood" this suggests a disturbance in the mechanism of the production of lysolecithin following splenectomy.

13. *Animal experiments:* Additional experiments were carried out in 3 dogs, 8 guinea-pigs, and 1 rabbit, in all of which hematologic studies were made before and after splenectomy. In general, the results in these normal animals were identical with those found in the human cases. In the dogs, target cells became extremely prominent. Thus in Dog 1, the peak target cell count was 72%, 109 days after splenectomy; 162 days after operation, the target cell count had become stabilized at approximately 33%. There was no anemia at this time and the hypotonic fragility was definitely decreased (from control 0.56% to 0.26%, to 0.44% to 0.16%). Howell-Jolly bodies were also present and there was marked leukocytosis. In the guinea-pigs, the percentage of target cells approximated that found in the human (5% to 10%) with an associated diminution in hypotonic fragility, but the outstanding feature was the extreme thrombocytosis. In the rabbit, an extreme increase in platelets was also present, but even after 4 months, target cells were few in number and the hypotonic fragility was not increased.

Discussion. *Analysis of Results and Discussion of Literature.* The most important reviews dealing with the effects of splenectomy are those of Pearce, Krumbhaar, and Frazier²⁸ (1914); Krumbhaar²¹ (1932); and Lauda²² (1933). Our studies, which deal chiefly with the hematologic findings in a series of splenectomized humans, are in general confirmatory of previous findings and add a few details based on recently developed hematologic methods. In the review of Pearce, Krumbhaar and Frazier,²⁸ the effects of splenectomy in normal dogs are carefully studied. In the main, three results were noted: a varying degree of transient anemia, increased hypotonic resistance of the erythrocytes, and a diminished tendency for the development of jaundice when hemolytic agents were administered. Much emphasis is laid upon the anemia which was commonly present for several weeks. Krumbhaar's²¹ review of 1932 again stresses the anemia, which at least indirectly is stated to be associated with the increase in red cell resistance. The monograph of Lauda²² on the physiology

of the spleen is a carefully documented and critical review of all the knowledge of splenic physiology to 1933, together with a very complete bibliography. The final chapter is devoted to a discussion of evidence for and against the likelihood that internal secretions of the spleen exist.

1. *Hemoglobin and Red Cell Count.* No really definite anemia was present in our uncomplicated cases, which were studied at varying intervals (4 weeks to 15 years) after splenectomy. Although Krumbhaar²¹ and a number of other investigators found anemia after removal of the normal spleen, it should be noted that this finding has frequently failed of confirmation; indeed, polycythemia has at times been noted. The contradictory results,* as Lauda²² points out, are at least partly due to differences in animals, techniques, diets, the length of time that had elapsed after splenectomy and so on. At any rate, the anemia in the splenectomized dogs was transitory and probably without bearing on the question of red cell resistance, Howell-Jolly bodies, and so on. This is shown by the presence of these abnormalities in our cases, although anemia was absent.

2. *Leukocytes.* A persistent leukocytosis which was present in one-half our cases was due chiefly to an absolute increase in lymphocytes, monocytes, and to a lesser extent in eosinophils. The reasons for these findings are not clear, although they have repeatedly been noted (cf. Naegeli²³).

3. *Platelets.* Thrombocytosis was present in many of the cases. The striking increases in platelets which follow splenectomy have been known for many years. Our studies in thrombocytopenic purpura have led us to conclude that the spleen normally exhibits an inhibitory effect upon platelet production in the bone-marrow. When this effect is removed, platelet production becomes greatly increased.

4. *Changes in the Red Cells.* (a) The most constant hematologic finding in our splenectomized material was the presence of Howell-Jolly bodies, first described by Hirshfeld and Weinert^{18,19} and confirmed since in many investigations. The Howell-Jolly body appears to be a nuclear fragment in an otherwise fully mature erythrocyte. Although there is still some discussion as to the method of nuclear removal from the most mature normoblast, most authorities are in accord in believing that the nucleus is extruded *en masse* rather than by fragmentation. If this is correct, the presence of Howell-Jolly bodies would indicate, as pointed out by Hirshfeld and Weinert,^{18,19} an abnormality in nuclear extrusion, and their

* The increase in the red cell count that some authors have observed after splenectomy is sometimes best explained on the basis of removal of a diseased spleen in the presence of an existing anemia. While there is not much evidence for removal of a normal spleen causing polycythemia (other than that of brief postoperative change in cell concentration), this procedure does not appear to cause either marked or lasting anemia.—EDITOR.

appearance after splenectomy, a control of this function by the spleen. This theory, which was the first to express a possible hormonal regulation by the spleen of a bone-marrow function, was apparently substantiated by the experiments of Lauda and Flaum.²³ These authors regularly observed Howell-Jolly bodies in splenectomized rats. When 2 rats were joined in parabiosis and the spleen of one of the partners removed, no Howell-Jolly bodies were observed. However, when the second partner was also splenectomized the blood of both showed erythrocytes with Howell-Jolly bodies. Erythrocytes containing these abnormal nuclear fragments are occasionally seen in conditions other than following splenectomy. Thus, Ching and Diggs⁷ found these cells in certain cases of sickle cell anemia, and they have been observed in other conditions.

(b) *Target Cells and Increased Resistance of the Red Cells to Hypotonic Solutions.* The cause of the increased hypotonic resistance of the red cells after splenectomy has occasioned a great deal of speculation. Bottazzi,⁶ who first observed this phenomenon in 1894, considered three possibilities: (1) anemia; (2) the presence of more resistant red cells arising from a rapidly growing bone-marrow; (3) the presence in the spleen of a special function to weaken certain red cells. Of these possibilities, he considered the third the most likely and accordingly postulated for the spleen a "hemacatatonistic" function. Pearee, Krumbhaar, and Frazier²⁸ believed that the increased resistance was probably associated with the anemia; the increased resistance in cases without anemia or after the anemia had disappeared was not adequately explained. Banti¹ and others postulated that the spleen possessed a hemolyzing function, and a number of workers have observed that red cells from the splenic vein were definitely more fragile than those from the splenic artery. In recent years, the work of Bergenhem and Fåhræus⁵ pointed to the possibility that the activity of "lysolecithin" in the relatively stagnant blood of the spleen might increase erythrocyte fragility. Ham and Castle¹⁵ have recently concluded that the spleen is the chief "stasis" organ of the body and that there, as the result of at first purely physical and later of metabolic changes, the red cells become spheroidal and thus more readily destructible. Knisely's^{20a, b} histologic studies in the living animal have beautifully demonstrated that blood, free of plasma, stagnates in splenic sinusoids for several minutes to several hours. Thus numerous studies bearing directly or indirectly on the problem, indicate that the red blood cells become modified in their passage through the spleen and that the modification is in the direction of increased spheroidicity and increased hypotonic fragility.

A definite morphologic basis for the increased hypotonic resistance of the erythrocytes after splenectomy has only recently been established. Barrett³ noted the presence of "bull's eye" or "target types" of red blood cells in many cases of obstructive jaundice.

Because increased resistance of the red cells was simultaneously present, the possibility that these two abnormalities were related was suspected and careful studies brought out clearly that the more resistant red cells were indeed the target cells. Barrett³ found that these cells were present chiefly in four groups of cases: (1) obstructive jaundice; (2) hypochromic anemia; (3) following splenectomy, and (4) in steatorrhea. His studies indicated that the target cell was thinner than the normal red cell and thus could imbibe more water before bursting (hemolyzing) in hypotonic solutions of salt. Thus, the target cell with *decreased* hypotonic fragility may be said to be the antithesis of the small, thick spherocyte of hemolytic jaundice with *increased* hypotonic fragility.

Following splenectomy in acute hemolytic anemia (hemolytic icterus of the *acquired* variety) it was noted that when the patient recovered, the hypotonic *resistance* of the red cells was increased and target cells were present. However, the splenectomized cases of congenital hemolytic jaundice, whether in crisis or otherwise, continued to show an increase in hypotonic *fragility* of the erythrocytes and target cells were absent. This has already been noted by Heilmeyer¹⁶ and Dameshek and Schwartz¹⁰ as an additional differential feature between the congenital and acquired cases of hemolytic jaundice.

It seems likely therefore that in the absence of the spleen, the red cell population tends on the whole to be thinner than normal. Although the red cells vary slightly in degrees of thickness, as in diameter, cells thin enough to be called "target cells" are few. With the spleen removed, there is probably a shift to a thinner population with a definite proportion (3% to 20%) of the erythrocytes becoming thin enough to be recognized as target cells. A definite and striking reduction in mean corpuscular thickness in our cases was not observed, although in general a tendency to diminished values was present. In congenital hemolytic jaundice, with thick cells being persistently formed, the reversion to somewhat diminished thinness after splenectomy is not sufficient to result in the appearance of target cells, as in the acquired cases. The probable reduction in erythrocyte thickness after splenectomy indicates that the spleen normally causes increased spheroidicity of the red cells. The exact mechanism of this action has not as yet been clarified.

(e) *Hemolytic Index.* Possibly related to the increased resistance of the red cells after splenectomy is the lowered hemolytic index, which was found in nearly two-thirds of our cases. This finding apparently persists for many years after operation, since it was present in Cases 1 and 9, splenectomized respectively 8 years and 15 years previously. As previously pointed out, the hemolytic index relates the urobilinogen excretion to the amount of pigment (total hemoglobin) from which it is derived. The total hemoglobin may be said to be a function of the individual's surface area. Normally

the hemolytic index demonstrates that 100 gm. of hemoglobin yield about 10 to 20 mg. of fecal urobilinogen per day. Heilmeyer and Oetzel¹⁷ found that 10.3 to 22.8 mg. of urobilinogen were excreted for each 100 gm. of hemoglobin (using 16.5 gm. hemoglobin as 100%). In our investigations, figures of 11.1 to 20.8 mg. were obtained (15.5 gm. hemoglobin = 100%). That the hemolytic index is a much better indicator of the degree of blood destruction than the fecal urobilinogen output itself is brought out in Case 3, a small boy aged 10. Here, although the urobilinogen excretion was only 29.4 mg., a figure definitely lower than normal, the index of 14.6 mg. demonstrated a normal output of pigment. Only with the use of the hemolytic index is it possible to obtain a definite interpretation of the degree of destruction, particularly in small individuals and in anemia, providing, to be sure, that all the other factors of importance in urobilinogen metabolism are taken into consideration.

That the urobilinogen output in the feces may be diminished after splenectomy has occasionally been observed in previous investigations (Pearce, Krumbhaar, and Frazier,²⁸ Lichtenstein and Terwen,²⁴ Paschkis,²⁷ Barker,² Watson, *et al.*^{33b} Singer,^{31a} in an experimental study, found a decrease in fecal urobilinogen output amounting to about one-half the preoperative value in 50% of his splenectomized dogs. The remaining dogs failed to show any considerable change. In most of the recorded human cases, the diminished output after splenectomy was studied in patients with hemolytic anemia in which prior to splenectomy there is a greatly increased blood destruction. In our cases, normal indices after splenectomy were present in a case of Gaucher's disease and in 2 cases of congenital hemolytic jaundice (where the normal index may indeed indicate slightly increased hemolysis for a splenectomized patient). All the other cases had a low hemolytic index (with the exception of Case 15—continuing hemolysis—and the possible exception of Case 5—11.4 mg.).

Of interest was the fact that 2 of the 4 cases of congenital hemolytic jaundice showed, despite the continued presence of spherocytosis, a *low* hemolytic index. From these observations alone it would appear that spherocytes, despite their abnormal fragility to hypotonic saline, are no more readily destroyed than normal erythrocytes.

The urobilinogen excretion in the feces is the end-result of a very complicated process, and one can therefore not conclude that the urobilinogen excretion is a direct measure of hemoglobin destruction. Theoretically, the low hemolytic index found after splenectomy could be due to various causes: (1) diminished blood destruction; (2) a disturbance in the ability of the body to form bilirubin from liberated hemoglobin; (3) an increased storage of pigment. Of these possibilities, the first, namely a reduction in the breakdown of

hemoglobin, appears to be the most likely. The question arises whether the formation of target cells (which are more resistant toward hypotonic saline) may be directly correlated with the lowered hemolytic index. No direct parallelism was, however, demonstrable between the actual number of target cells and the degree of the diminution in urobilinogen output. A *general* diminution in thickness, not directly measurable, may be of greater importance in this connection than the finding of large numbers of target cells. It should be noted that target cells are present in considerable numbers in sickle cell anemia and in Cooley's anemia, conditions associated with a greatly *increased* hemoglobin destruction. Furthermore, the presence of a low hemolytic index is by no means specific for the postsplenectomized state, as this finding is present to some extent in other conditions as in iron deficiency anemia, polycythemia, hypothyroidism, and so on (*cf.* Paschkis,²⁷ Watson^{33b}). In these conditions, however, the lowered hemolytic index can probably be interpreted as denoting an imbalance between erythrocyte formation and destruction. This will be discussed in a later paper.

5. *Studies of the lysolecithin metabolism* in our cases revealed two disturbances, *i. e.*, a frequent lack of increase of lysolecithin in the serum upon incubation and a low absolute value of lysolecithin in the peripheral blood. The latter observation has been confirmed by Gripwall.¹³ It is apparent from these observations that splenectomy frequently leads to a disturbance of the whole mechanism of lysolecithin production.

In summary, therefore, our studies of the splenectomized individual have frequently revealed: (1) leukocytosis due primarily to an increase in lymphocytes and monocytes; (2) thrombocytosis; (3) qualitative morphologic changes in the erythrocytes—notably the presence of Howell-Jolly bodies, and target cells; (4) increased hypotonic resistance of the erythrocytes; (5) a diminution in the hemolytic index as evidenced by the relationship of the fecal urobilinogen output to the total mass of hemoglobin, and (6) disturbances in the lysolecithin metabolism.

If one takes 7 (Table 4) abnormalities which are frequently present following splenectomy (leukocytosis, thrombocytosis, Howell-Jolly bodies, target cells, increased "minimal" hypotonic resistance, lowered hemolytic index, and altered lysolecithin metabolism) and assigns to each a score of 1, a score of 7 was obtained in 1 case, and a score of 6 in 6 cases. In 3, there was a score of 5 and in 1 (a case which had been splenectomized 15 years previously), a score of only 2 was obtained. In Cases 5, 11 and 13 the data were incomplete. A normal individual has a score of 0. A score of 5 or over in a group of 7 possible factors may thus be indicative of the splenectomized state (and perhaps of a "hyposplenic" condition).

That this grouping of characteristics is *specific* for splenectomy is as yet not certain. It is possible that other conditions will be

found in which scores of "5" or over are present. Our studies have thus far, however, failed to demonstrate this. For example, in cirrhosis of the liver, in which target cells and increased resistance of the red cells are common, there is generally leukopenia, thrombocytopenia, absence of Howell-Jolly bodies, a variable hemolytic index, and a normal lysolecithin metabolism (score of 2). In Cooley's anemia and "target cell" anemia,^{9b} again although target cells and increased resistance are common, none of the other factors is usually present, and what is more the hemolytic index is very high. The same holds true for sickle cell anemia, in which the added factor of Howell-Jolly bodies may be present, as well as occasional leukocytosis (highest possible score 4). In polycythemia, leukocytosis, thrombocytosis and diminished hemolytic index are frequently present, but the remainder of the 7 factors are all normal. In chronic "primary" hypochromic anemia, target cells, increased resistance, and diminished hemolytic index may all be present but there is usually leukopenia and thrombocytopenia and the remaining factors are normal. In a case of probable splenic vein thrombosis, there was diminished hemolytic index and changes in the lysolecithin metabolism (score of 4), but leukopenia and thrombopenia were present. Although this scoring of abnormal factors is interesting, we recognize the danger of placing any great reliance on numerical systems of this sort. We have found it of some use to us, at least at present, in evaluating the evidence obtained in the cases studied in this investigation.

TABLE 4.—"SCORE" OF POST-SPLENECTOMY FACTORS.

Factors.	Normal.	Case 1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
Increased W.B.C.	—	+	+	+	+	+	—	+	—	—	+	+	+	—	+
Increased platelets	—	—	+	+	—	+	—	+	—	—	—	+	—	—	—
Howell-Jolly bodies	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Target cells	—	+	+	+	+	+	+	+	+	—	+	+	+	+	+
Increased minimal saline resistance	—	+	+	+	+	+	+	+	+	—	+	+	+	+	+
Diminished hemolytic index	—	+	+	—	+	—	+	+	+	+	+	+	+	+	—
Disturbed lysolecithin metabolism	—	+	—	+	+	Not done	+	+	+	—	+	Not done	+	Not done	+
Score	0	6	6	6	6	5 of 6	5	7	5	2	6	6 of 6	6	4 of 6	5

The Concept of "Hyposplenism" and "Hypersplenism." In the course of our studies, we observed a case of obscure refractory anemia in which the score of abnormal factors was 4 (of the 6 factors tested). Howell-Jolly bodies and target cells were common and the hemolytic index was very low. Unfortunately, the lysolecithin

tests could not be done and a postmortem examination was not obtained. The tentative diagnosis of a possible "hyposplenic" state was made. Both Schur³⁰ and Schilling²⁹ made the diagnosis of possible atrophy of the spleen in 2 non-splenectomized cases showing large numbers of Howell-Jolly bodies. In Schilling's case, a postmortem examination was performed and showed definite atrophy of the spleen. In this connection, it should be noted that target cells are common in sickle cell anemia, in which the spleen is not infrequently atrophied.

In studies of a case showing large numbers of target cells ("target cell anemia"³⁶) and many features of Cooley's erythroblastic anemia (without erythroblasts in the peripheral blood) the possibility of a "hyposplenic" condition was postulated. Target cells were also found in considerable numbers in typical cases of Cooley's anemia and in sickle cell anemia. That Cooley's anemia, "target cell" anemia, and sickle cell anemia (hemolytic syndromes unaffected by splenectomy, and with increased hypotonic *resistance*) are related diseases with the target cell as the common denominator was broached as a possibility.

That "hypersplenic" conditions may also be present is not beyond the realm of possibility. It would appear likely, as stated above, that the spleen has a "reciprocal" relationship to the bone-marrow. The increase in leukocytes and thrombocytes after splenectomy, the appearance of both Howell-Jolly bodies and target cells, all suggest this relationship. It is conceivable that splenic hyperactivity might result in a greater than normal effect upon the marrow. Were this so, leukopenia, thrombocytopenia, and increased hemolysis might result. It is interesting that in many instances of splenomegaly for whatever cause (cirrhosis of the liver, "chronic congestive splenomegaly," the Banti syndrome, infections associated with splenomegaly, notably typhoid fever, miliary tuberculosis, and so on) leukopenia and thrombocytopenia are common. To speculate further, splenic "hyperactivity" may be "total" or limited to one function ("selective"). For example, idiopathic thrombocytopenic purpura may be due to greatly increased activity of the platelet inhibiting function and hemolytic anemia to a greatly increased hemolytic function.

The possibility that splenic hormones of various types exist, some of them affecting the bone-marrow, has already been broached. The presence of Howell-Jolly bodies (improper denucleation?) after splenectomy suggests a possible relationship of the spleen to extrusion of the normoblast nucleus. Persistent leukocytosis after splenectomy suggests a relationship (inhibitory?) to leukocyte formation, and persistent thrombocytosis an inhibitory or regulatory relationship to megakaryocyte-platelet formation. These possibilities are deserving of future investigation.

Summary. A hematologic study was made of 19 patients in whom splenectomy had been performed from 4 weeks to 15 years previously. A rough grouping of cases into non-hemolytic and hemolytic was made. Particular attention was paid to the question of "target" cells and increased hypotonic resistance; the fecal urobilinogen output and the "hemolytic index"; and the "lysolecithin" metabolism.

Howell-Jolly bodies in erythrocytes were a constant finding after splenectomy, and target cells—abnormally thin red cells—were usually present. The presence of the latter, together with a tendency to thinness on the part of the whole red cell population adequately accounts for the increased hypotonic resistance usually seen and is confirmatory of previous work indicating that the spleen makes red cells thicker and more fragile to hypotonic salt solutions.

A lowered urobilinogen output in the feces was commonly found after splenectomy, indicating a diminution in hemoglobin destruction, perhaps related to increased thinness of red cells. The "hemolytic index" is regarded as a more important indication of hemoglobin destruction than the urobilinogen output alone. This index is determined from knowledge of the daily fecal urobilinogen output and the total circulating mass of hemoglobin (as determined from blood volume estimations).

The lysolecithin metabolism showed definite alterations after splenectomy. These observations are confirmatory of the contention of Bergenhem and Fåhræus who believe that this normal serum lysin is produced in the spleen.

Leukocytosis and thrombocytosis were commonly present. These findings, together with the appearance of Howell-Jolly bodies (inadequate denucleation?) suggest that splenectomy may result in the removal of certain normal inhibitory mechanisms of the spleen upon the bone-marrow.

The splenectomized state is thus characterized by the presence of a group of several abnormal factors. The possibility that "hyposplenic" and "hypersplenic" conditions are occasionally present is discussed, together with evidence indicating a hormonal regulation of certain bone-marrow functions by the spleen. These observations of splenectomized individuals indicate that the spleen has direct effects on the red cells which traverse its sinusoids and indirect effects on the hematopoietic cells of the bone-marrow.

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HEMOPHILUS INFLUENZÆ TYPE A ENDOCARDITIS.

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EVER since the description of the so-called "influenza" bacillus by Pfeiffer¹⁹ in 1893, reports of endocarditis caused by this organism have appeared from time to time. The disease, however, is apparently not common, because less than 40 well-authenticated cases have been recorded during the half century which has since elapsed. Austin¹ and Jehle¹² furnished the first clinical reports of influenzal endocarditis, and Horder¹¹ in 1909 regarded it as second only to streptococcal endocarditis in prevalence. This opinion was later favored by Libman¹⁴ and Blumer², both of whom thought the influenza bacillus to be responsible for most of the cases of endocarditis not caused by streptococci. More recently, Thayer²⁵ estimated that only about 2.5% of all cases of endocarditis are caused by the influenza bacillus, which he ranked fifth in order of importance, giving precedence to the streptococcus, staphylococcus, pneumococcus, and gonococcus. Judging from the infrequency with which the disease has been reported, however, it would seem that even Thayer's relatively low figure may be somewhat too high.

In 1918 Malloch and Rhea¹⁶ pointed out that many alleged cases of influenzal endocarditis probably represented errors in diagnosis due to inaccurate or inadequate bacteriologic study. Such errors obviously were unavoidable at that time since little was known

concerning influenza bacilli beyond the facts that they were Gram negative, hemophilic, and apparently antigenically heterogeneous. However, the study of accessory growth factors by Davis,⁵ Thjötta and Avery,²⁶ Kristensen,¹³ Rivers,^{23a,b} and Fildes,^{9a} soon afterwards disclosed that important differences among organisms of the hemophilic group could be detected by their behavior on media containing the now well known "X" and "V" factors. Moreover, certain strains of influenza bacilli were shown by Pritchett and Stillman²² and by Fildes^{9b} to possess hemolytic properties. This information formed the basis for a classification of the *Hemophilus* group, proposed by Valentine and Rivers²⁸ in 1927, which is now generally accepted and is reproduced, with slight modification (Table 1). According to this classification, strains of influenza bacilli may be sharply divided into two main groups: (1) *Hemophilus influenzae*, which require both "X" and "V" factors for growth, and (2) *Hemophilus para-influenzae* which require only the "V" factor.

TABLE 1.—CLASSIFICATION OF THE HEMOPHILUS GROUP.

- A. Requiring both X and V* factors: *Hemophilus influenzae*
 - 1. Non-hemolytic
 - 2. Hemolytic
- B. Requiring only V factor: *Hemophilus para-influenzae*
 - 1. Non-hemolytic
 - 2. Hemolytic
- C. Requiring only X factor: *Hemophilus canis*
- D. Requiring neither X nor V factors: *Hemophilus pertussis*

* The "X" factor is heat-stable and associated with the iron-bearing portion of the hemoglobin molecule. The "V" factor is heat-labile and has been found by Lwoff and Lwoff¹⁶ to be identical with Warburg's co-enzyme.

For many years influenza bacilli were thought to be antigenically heterogeneous, but not long ago Pittman²⁰ and Platt²¹ showed that freshly isolated "smooth" strains of *H. influenzae* develop capsules which contain specific soluble substances of carbohydrate nature, in a manner similar to pneumococci. Such strains may be divided by serologic methods into 6 types, designated a, b, c, d, e and f. More recently, Chandler, Fothergill, and Dingle³ demonstrated that *H. influenzae* exhibits the M-S-R variation of Dawson,⁶ and that capsules are produced and type-specificity is developed only in the mucoid phase. These important findings readily explain the observation, emphasized by Topley and Wilson,²⁷ that apparently smooth strains of *H. influenzae* frequently are antigenically non-specific. So far as is known, strains of *H. para-influenzae* never develop a mucoid phase and are therefore never type-specific. A summary of the important differences between *H. influenzae* and *H. para-influenzae* is given in Table 2.

In the light of these facts concerning influenza bacilli it is of interest to note that all adequately studied cases of influenzal endocarditis thus far reported have been found to be caused by *H. para-influenzae*, and according to Miles and Gray¹⁷ there is no

case on record in which *H. influenzae* which required both "X" and "V" growth factors has been isolated from an endocardial infection. Recently this opinion was endorsed by Craven, Poston, and Orgain,⁴ who carefully reviewed the literature, and were able to collect only 36 cases, including 2 of their own, in which the clinical, pathologic, and bacteriologic data were sufficient to warrant the diagnosis of influenzal endocarditis. Craven and his colleagues state, indeed, that the 4 cases reported by Miller and Branch,¹⁸ DeSanto and White,⁸ and Fothergill *et al.*,¹⁰ were caused by hemolytic *H. influenzae* which required "X" and "V" factors, but they agree that there are no cases which fulfill the requirements for inclusion in the non-hemolytic group. However, an examination of the papers by Miller, DeSanto, Fothergill, and their associates, reveals no mention whatever of the use of "X" and "V" media, and moreover, in the opinion of the author, the organisms which they described were probably *H. para-influenzae*.

TABLE 2.—COMPARISON OF HEMOPHILUS INFLUENZÆ WITH HEMOPHILUS PARA-INFLUENZÆ.

	<i>H. influenzae</i> .	<i>H. para-influenzae</i> .
Morphology	Cocco-bacilli with occasional rods and filamentous forms	Marked pleomorphism; rods and filaments predominate
Accessory growth factors	Requires both "X" and "V" factors	Requires only "V" factor
Action on blood agar	Usually non-hemolytic	Not infrequently hemolytic
Action on carbohydrates	Fermentative powers usually slight	Usually wider range of fermentative powers
Action on tryptophan	Most strains produce indole	Most strains fail to produce indole
Pathogenicity for animals	Mucoid strains pathogenic for mice and rabbits	Comparatively less pathogenic for mice and rabbits
Antigenic classification	Mucoid strains elaborate capsules containing specific soluble substances and may be classified antigenically as Types a, b, c, d, e, and f	Antigenically heterogeneous; no capsule formation

Since no authentic case of bacterial endocarditis caused by typical *H. influenzae* has been previously recorded, it has been impossible, as pointed out by Miles and Gray,¹⁷ to compare the known para-influenzal endocarditis with the influenzal variety. The following example of true influenzal endocarditis is therefore reported.*

Case Report. H. R., No. 588159, a 19-year-old, single, electrical worker, was admitted to the Presbyterian Hospital on August 25, 1939. The patient's chief complaints were weakness, fatigue, and night sweats of 3 months' duration. He had also had fever for 1 week prior to admission.

One brother developed rheumatic heart disease when 5 years old and died at the age of 22, apparently of subacute bacterial endocarditis. The remainder of the family history was non-contributory.

The patient had in general enjoyed good health until the onset of the present illness. He had never suffered from any acute infectious diseases

* The author is indebted to Dr. Robert F. Loeb and Dr. James W. Jobling for permission to report this case.

of note. At the age of 9 he was seen in the Vanderbilt Clinic with complaint of swelling and stiffness of the right knee. He was found to be afebrile but no other details of this incident remain available. Two years later, when aged 11, he was treated in the clinic for an acute left maxillary sinusitis which rapidly subsided. Examination of the heart and lungs at that time revealed nothing definitely abnormal. Throughout the succeeding 8 years he apparently enjoyed excellent health and was able constantly to participate in various forms of strenuous athletics.

Three months before entry the patient suddenly developed excruciating pain in the left cheek. Examination showed some tenderness over the left maxillary region, and the Roentgen ray revealed slight clouding of the left antrum. The antrum was punctured for drainage, but the washings appeared clear and unfortunately no culture was taken. The pain subsided within a few days without further treatment. Shortly following this episode the patient noted gradually increasing weakness, lethargy, and fatigue, accompanied by frequent drenching night sweats. Three weeks before admission his right ankle became painful, hot, and swollen. He was seen at another hospital where a diagnosis of rheumatic fever was made. The swelling and pain in the right ankle gradually disappeared over a period of 2 weeks. Nine days before entry the patient was seen in the dispensary, where examination of the heart and lungs disclosed no abnormal findings. Weakness, fatigue, and night sweats continued, and for the week previous to hospitalization he had a constant fever ranging as high as 103°F .

Physical Examination. On admission the temperature was 101.2°F ., pulse 90, respirations 20, and blood pressure 140/40. Examination revealed a well-developed and nourished white male who did not appear acutely ill. There was no dyspnea, orthopnea, cyanosis, edema, or jaundice. A visible pulsation was noted in the suprasternal notch. The mucous membranes appeared somewhat pale. No petechiæ could be discovered. The finger-tips were neither clubbed nor tender.

The heart was enlarged to the left by percussion and a forceful, heaving apex impulse was palpated 12 cm. to the left of the midsternal line in the 5th interspace. On auscultation over the apical area there was a faint, short, pre-systolic murmur with a snapping first sound, followed by a loud, blowing systolic murmur transmitted to the left axilla. A rumbling diastolic murmur in early and mid-diastole was also detected. Over the aortic area could be heard a rather harsh systolic murmur, transmitted well to the neck vessels, followed by a blowing diastolic murmur which almost completely obliterated the second sound. The lungs were clear. The pulse was of the Corrigan type.

The abdomen was relaxed and soft. The liver could not be palpated and was not enlarged to percussion. The spleen was slightly enlarged, firm, smooth, and non-tender. The remainder of the physical examination was not remarkable.

Laboratory Findings. Examination of the blood revealed a hemoglobin of 9.5 gm. (Sali), an erythrocyte count of 3,900,000, and a leukocyte count of 9600. The differential count showed neutrophils 77%, lymphocytes 17%, monocytes 5%, and eosinophils 1%. The erythrocyte sedimentation rate was 80 mm. in 1 hour, using the Westergren method. The Kline test was negative. The urine showed no albumin, sugar, or casts, and contained only a few leukocytes. A Roentgen ray film of the chest taken at a distance of 2 meters showed an enlarged cardiac silhouette with the following measurements: MR 3.5 cm., ML 10.8 cm., TD 14.3 cm., GV 5.8 cm. The internal diameter of the chest was 27.5 cm. The configuration of the heart shadow suggested that seen with aortic valvular lesions. The electrocardiogram exhibited form changes indicative of definite heart muscle damage. The P-R interval was 0.15 seconds, with normal sinus rhythm. A blood

culture taken on the day of admission showed no growth after incubation for 2 weeks.

The admission diagnosis was: Rheumatic heart disease, mitral stenosis and insufficiency, aortic stenosis and insufficiency, subacute bacterial endocarditis.

Course. During the patient's first admission he had surprisingly few symptoms and in general his condition remained good. He did, however, have a constantly elevated rectal temperature ranging from 99.6° to 101.8° F. The leukocyte count, repeated at frequent intervals, was moderately elevated from 11,480 to 16,150, with 67 to 77% neutrophils. The diastolic pressure remained constantly low, and the blood pressure readings varied between 120/25 to 140/40. From time to time he complained of feeling weak and tired, and occasionally he had a profuse diaphoresis associated with upward swings in temperature.

Four days after entry (Aug. 29) localized areas of tenderness developed suddenly over the left elbow and at the tip of the left index finger, with slight redness and swelling. Two days later the spleen was found to be somewhat larger, but still non-tender. Petechiæ appeared for the first time in the lower conjunctivæ on Sept. 10. Meanwhile the auscultatory findings in the heart had changed, and the snapping apical first sound could no longer be heard, while the heart tones at the apex had become almost entirely replaced by a continuous murmur.

In spite of the apparently clear-cut evidence of bacterial endocarditis, 6 blood cultures taken between the date of admission and Sept. 11 all failed to show growth, although none was discarded before 2 weeks of incubation.

Chemotherapy with sulfanilamide was begun Aug. 30 and continued until the patient's discharge, 52.8 gm. being administered over a period of 12 days. Blood concentrations of the free drug ranged from 3.0 to 6.4 mg. per 100 cc. The sulfanilamide was well tolerated, but it failed completely to effect any improvement in the condition of the patient.

Arrangements in the meantime had been made for terminal care and the patient was discharged to his home on Sept. 11, the 18th hospital day, with admission diagnosis unchanged.

Interval Note. The patient was seen in the Vanderbilt Clinic on Sept. 21, at which time he had gained 9 pounds and stated that he felt much better. However, on the preceding evening he had experienced a sudden, sharp pain in the right heel followed by a temperature rise to 102° F. He was seen again a week later, and still felt fairly well, but temperature had remained elevated, with daily rises to 101° to 102° F. On physical examination no new findings were observed. The hemoglobin was 13.1 gm., erythrocyte count 4,850,000, and leukocyte count 11,800 (neutrophils 70%, lymphocytes 24%, and eosinophils 6%). The erythrocyte sedimentation rate had dropped to 35 mm. in 1 hour. A blood culture again failed to show growth.

On Oct. 14, 5 weeks after discharge, he suddenly developed severe pain in the left upper quadrant, unaccompanied by nausea or vomiting. The pain continued without relief, and shortly thereafter he returned to the hospital.

Final Admission. The patient was readmitted on Oct. 17, 1939. On entry the temperature was 102° F., pulse 120, respirations 26, and blood pressure 130/0.

Physical Examination. The patient now appeared acutely ill with marked pallor and cyanosis of the skin and mucous membranes. There was moderate dyspnea and orthopnea. Petechiæ were noted in the lower conjunctiva of the right eye. Capillary pulsation could be readily seen in the nail beds. The heart was enlarged 12 cm. to the left in the 5th interspace

with a heaving apical in pulse. On auscultation at the apex a short pre-systolic murmur was heard, followed by a loud, harsh systolic murmur well transmitted into the left axilla. Over the base a harsh systolic murmur was heard, followed by a short, high-pitched diastolic whiff. No pericardial friction rub could be detected. The lungs were clear except for a few frank medium râles at the left base posteriorly. The abdomen was moderately distended. A smooth, slightly tender liver was palpated 4 finger-breadths below the right costal margin. A tender, moderately enlarged spleen could also be felt. No other significant observations were made on physical examination.

Laboratory Findings. The blood showed a hemoglobin of 11.0 gm., erythrocyte count 4,570,000, and leukocyte count 23,840 (neutrophils 86%, lymphocytes 11%, monocytes 2%, and eosinophils 1%). The erythrocyte sedimentation rate was 45 mm. in 1 hour. The urine contained 1+ albumin and numerous granular casts, but no leukocytes or red cells. A blood culture yielded growth of *H. influenzae* in both flasks after incubation for 4 days.

Course. On admission the patient was restless and apprehensive with almost complete disorientation. Dyspnea and cyanosis were marked, with the respiratory rate varying from 25 to 40 per minute, and oxygen therapy only slightly alleviated the respiratory distress. The rectal temperature remained elevated, ranging from 101.2° to 102° F.

On Oct. 18, the day following admission the patient was worse and the white count had risen to 38,900, with 89% neutrophils. Venous engorgement appeared marked and the dyspnea and cyanosis were unrelieved. However, the lungs were surprisingly clear.

On Oct. 19 the patient was rational and more comfortable. A portable Roentgen ray of the chest revealed cardiac enlargement and evidence of fluid at both bases. The findings in the electrocardiogram were strikingly different from those previously observed. Deformity of the QRS complexes was present in all leads with a prominent Q₁F. T₁, T₂, and T₄F were upright, while T₃ was inverted. The P-R interval was 0.16 seconds. The changes indicated a marked disturbance of ventricular conduction. The venous pressure was 310 mm. of water.

On Oct. 20 the patient was worse again and appeared very restless, as well as more dyspneic and cyanotic. The white blood count had further increased to 40,280, with 85% neutrophils. Examination revealed that while the upper trunk and extremities were cold, livid, and cyanotic, the legs and feet were warm and pink. The cyanosis of the lips, face, chest, and abdomen was striking. There was puffiness of the face and upper back with distention of the neck veins. The lungs were remarkably clear. The cardiac findings were unaltered. The liver was tender and enlarged to the level of the umbilicus. Following a brief period of augmented restlessness the patient suddenly expired.

Final Diagnosis. Rheumatic heart disease, mitral and aortic stenosis and insufficiency, subacute bacterial endocarditis, cardiac decompensation, chronic passive congestion of liver and spleen, infarction of spleen, and thrombosis of superior vena cava.

Autopsy. (Autopsy No. 13193, 2½ hours postmortem by Dr. W. H. Carnes). Examination was restricted to an 8-inch abdominal incision through which the contents of the thoracic cavity were removed en bloc, together with the aorta, trachea, and larynx. The pleural surfaces were smooth and there were no pleural adhesions. The pericardial cavity contained no excess of fluid and its surfaces appeared normal. The superior vena cava was removed in its entirety and contained no thrombus. The jugular veins were empty.

Heart. The heart was very large and weighed 510 gm. The epicardium itself was not remarkable, but near the apex of the heart, overlying the

anterior portion of the interventricular septum, there was a small, lenticular elevation about 5 mm. in diameter. Section through this showed an oval, encapsulated, reddish-gray mass of thrombus which appeared to lie in a tiny aneurysm of one of the coronary arteries.

On opening the heart both the right and left ventricles were found to be greatly dilated and hypertrophied. The right auricle appeared normal, but the left auricle was considerably dilated and showed hypertrophy of its wall. There were no thrombi in the auricular appendages. The tricuspid and pulmonary valves were normal. The aortic valve was anomalous and possessed but 2 cusps, the coronary arteries being centrally placed in the sinuses of Valsalva. The left cusp had been largely destroyed by a bacterial infection and was the seat of large, yellow, fungating vegetations which had completely replaced its posterior half. The vegetations had also spread upward into the neighboring sinus of Valsalva, and downward onto the

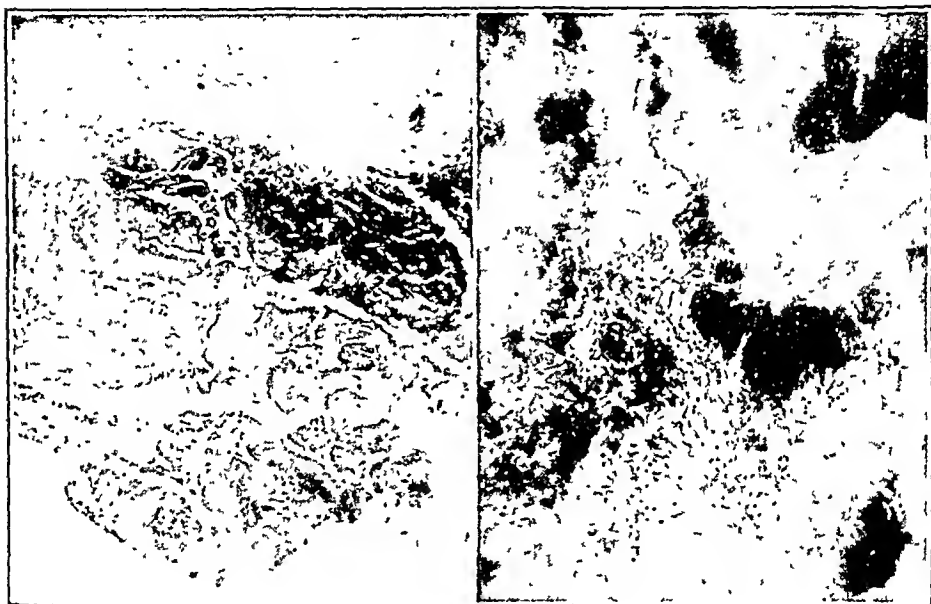


FIG. 1

FIG. 1.—Bacterial vegetation of aortic valve.

FIG. 2

FIG. 2.—*Hemophilus influenzae* in vegetation of aortic valve.

aortic leaflet of the mitral valve, which showed several small, unperforated mycotic aneurysms. The mitral valve was otherwise normal and there was no evidence whatever of antecedent rheumatic involvement.

Microscopic examination of a section made through the base of the aortic vegetation showed it to be composed of eosinophilic necrotic material almost devoid of cells, with patches of dense calcium deposition about its lower border (Fig. 1). Intermingled with these patches of calcification and covering virtually the entire surface of the vegetation were large colonies of bacteria. Sections stained with methylene blue, under higher magnification, showed masses of bacteria which exhibited mainly filamentous forms, although many coco-bacilli were also present (Fig. 2).

Gross examination of the ventricular myocardium revealed numerous small, pale, yellowish fat deposits, but in only one place in the middle portion of the left ventricular wall was there a pinkish, translucent area suggestive of a fresh scar. The apical portion of the left ventricle was very thin, no

doubt partly due to the dilatation, but possibly also the result of nutritional disturbances consequent to the small mycotic aneurysm of the coronary artery described near the tip of this ventricle. All of the coronary arteries were carefully opened in search for emboli, but no others were found which could be recognized with the naked eye.

Microscopic examination of sections removed from both ventricles, revealed numerous areas of fresh necrosis of the muscle, with loss of nuclei and increased eosinophilic staining of the cytoplasm (Fig. 3). Other areas of recent destruction still contained a few infiltrating inflammatory cells. One focus of older destruction showed mainly acellular connective tissue with numerous small blood-vessels (Fig. 4). In spite of the extensive myocardial damage bacterial emboli were found in only 2 small coronary arterioles. In addition a section through the small mycotic aneurysm at the apex of the left ventricle showed clearly the origin from the tiny coronary

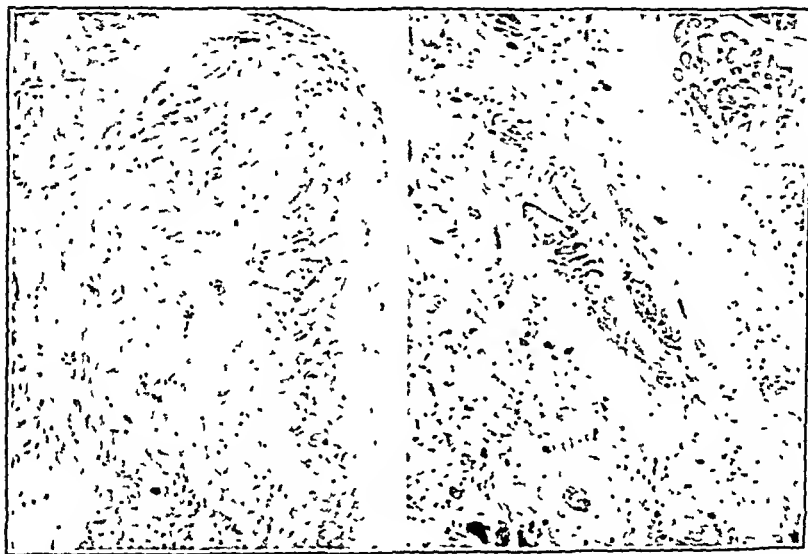


FIG. 3

FIG. 4

FIG. 3 —Focal necrosis of myocardium.

FIG. 4.—Healed focus of myocardial degeneration.

branch accompanying it. At the point of emergence of the vessel from the aneurysm its wall was greatly thickened eccentrically by a mass of calcified material. The aneurysm itself was entirely filled by old, autolyzing thrombus material in which no bacteria could be recognized (Fig. 5).

Sections through the interventricular septum showed changes similar to those observed in the ventricular myocardium, but less severe. The left auricle appeared normal.

Lungs. The right and left lungs weighed 540 gm. and 480 gm. respectively. On section the pulmonary tissue did not ooze fluid to any considerable extent, but there was a mottled, rusty appearance to the cut surface characteristic of chronic passive congestion. No areas of consolidation were seen and none of the vessels contained thrombi.

Microscopic examination showed all the alveoli to be filled with great number of large mononuclear phagocytes, which, however, contained little if any visible pigment. There was no edema.

Spleen. The organ was large and swollen, and weighed 380 gm. Beneath the capsule were irregular, raised areas varying from one to several centimeters in diameter, which on section proved to be rather fresh infarcts. The Malpighian bodies were unusually conspicuous. The splenic artery and vein appeared normal.

The microscope revealed marked chronic passive congestion, as evidenced by thick pulp cords and prominent distended sinusoids. The larger infarcts showed necrosis and considerable autolysis in their deeper portions; with scattered accumulations of neutrophils at their margins. Two fairly large branches of the splenic artery were plugged by organizing thrombi.

Liver. The liver weighed 2100 gm. and on section presented the classical "nutmeg" appearance of chronic passive congestion. Microscopic examina-

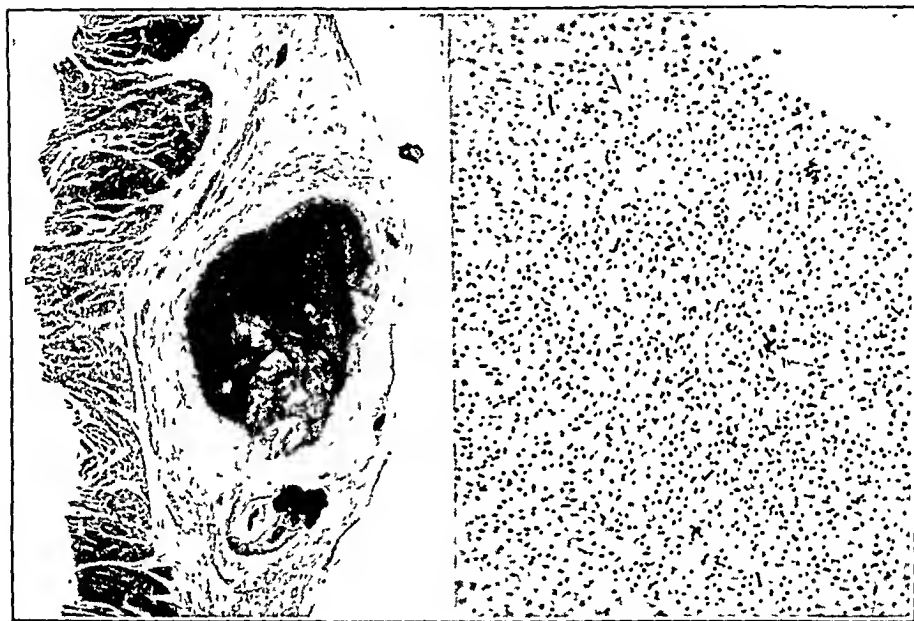


FIG. 5

FIG. 6

FIG. 5.—Mycotic aneurysm of coronary artery.

FIG. 6.—Gram-stained preparation of 18-hour culture of *H. influenzae* in Levinthal's broth.

tion showed large areas of atrophy or necrosis occupying the central portion of the lobules. There were hemorrhages into the collapsed framework where liver cells had disappeared.

Kidneys. The right and left kidneys weighed 185 gm. and 220 gm., respectively. The surfaces of each displayed large, pitted scars of healed infarcts measuring 1 to 3 cm. in their greatest dimensions. On section additional small, reddish areas of fresh infarction were seen. No hemorrhages were observed. The pelves, calices, and ureters were not unusual.

Microscopic section showed old and recent emboli in the interlobular arteries supplying the areas of infarction. Embolic lesions of the glomeruli were absent.

The remainder of the gross and microscopic examination failed to disclose anything of significance.

*Bacteriologic Findings.** The organism was isolated from both flasks of a blood culture taken on Oct. 17, 1939, 3 days before the death of the patient, and also from the heart's blood and a well-washed portion of aortic vegetation obtained postmortem.

For the antemortem blood culture two 5-cc. portions of the patient's venous blood were each seeded into 100 cc. of a beef heart infusion broth containing 1% neopeptone and 0.5% dextrose. In these cultures growth first appeared on the 4th day as a diffuse clouding of the media. Microscopic examination of Gram-stained preparations revealed numerous small Gram-negative bacilli and cocco-bacilli, with an occasional longer rod or filamentous form. Identical findings were obtained from a culture of heart's blood taken during the necropsy, as well as from a portion of the aortic vegetation which was repeatedly washed in saline and incubated in nutrient broth containing defibrinated rabbit's blood.

The results of further study of this strain may be summarized as follows:

Morphology. Repeated subculture on Levinthal's agar showed the morphology to be remarkably stable. Gram-stained smears of colonies chosen after 12 to 18 hours incubation invariably showed mainly small Gram-negative bacilli or cocco-bacilli with few rod or filamentous forms (Fig. 6).

Plain Agar. No growth.

Plain Broth. No growth.

Sheep Blood Agar. No growth. However, when plates were inoculated simultaneously with *Staph. aureus*, good growth occurred with typical satellite phenomena. No hemolysis.

Rabbit Blood Agar. Good growth in 18 hours. Colonies 0.5 to 1.5 mm. in diameter, tended to be confluent, and appeared flat, watery, and smooth, with slightly serrate edges. The cultures smelled strongly of indole. No hemolysis.

Levinthal's Agar. In 18 hours colonies were 1 to 3 mm. in diameter, flat, glistening, and somewhat opaque. By transmitted light the colonies showed marked iridescence. Odor of indole pronounced.

X and V Media. The results may be summarized in the following table:

<i>Media.</i>	<i>Growth.</i>
Nutrient agar + autoclaved Levinthal broth (X factor)	0
Nutrient agar + yeast extract (V factor)	0
Nutrient agar + autoclaved Levinthal broth + yeast extract (X + V factors)	++++

Fermentation Reactions. Fermentation tubes to which Levinthal's broth had been added were employed. The organism produced a small amount of acid from dextrose but did not attack mannite, lactose, saccharose, salicin, maltose, or xylose.

Indole Production. Large amounts of indole were formed in peptone water to which Levinthal's broth had been added.

Antigenic Classification. Organisms removed from cultures on Levinthal's agar at the end of 6 hours showed a clear-cut Quellung reaction with Type a *H. influenzae* rabbit antiserum. No capsule swelling was observed with Type b antiserum.

Precipitin reactions were also carried out with 6-hour cultures. Heavy suspensions of the organisms were made in normal saline, shaken thoroughly, and centrifuged. The clear supernatant fluid was then layered over Type a and Type b anti-sera. With the Type a serum a good immediate ring was observed, with heavy precipitate at the end of 24 hours. The reaction with Type b anti-serum was negative.

* The author wishes to thank Dr. Hattie Alexander and Miss Katherine C. Mills for their assistance in identifying the organism.

Pathogenicity. Unfortunately no adequate study was made of pathogenicity. One Swiss mouse inoculated intraperitoneally with 0.5 cc. of an 18-hour Levinthal broth culture succumbed within 24 hours. No other animals were inoculated.

Comment. The clinical course and pathologic findings in this case of *H. influenzae* endocarditis did not differ significantly from those observed by others in subacute bacterial endocarditis caused either by *H. para-influenzae*^{1,17} or *Strep. viridans*.^{2,25} The infection apparently originated in the maxillary sinus, with subsequent implantation on a congenitally anomalous aortic valve. This was followed by a prolonged febrile course, repeated embolic phenomena culminating in splenic infarction, and terminal acute myocardial insufficiency. In the final hours of the illness a rather striking polymorphonuclear leukocytosis developed, accompanied by physical findings suggestive of thrombosis of the superior vena cava. At necropsy, however, no thrombosis of this vessel could be demonstrated, and the lack of pulmonary edema, coupled with the evidence of marked passive congestion of the liver and spleen, indicate that these findings were due primarily to extreme right heart failure. The high leukocytosis must be explained chiefly on the basis of the extensive splenic infarction and necrosis, since elsewhere acute inflammatory changes were remarkably scant. The myocardium, while showing numerous areas of recent degeneration and scarring, showed fewer evidences of embolization of the coronary arteries than have been reported in *Strep. viridans* endocarditis.^{7,24} The one small mycotic aneurysm of a coronary arteriole was not of recent origin. The localization of the bacterial infection on the bicuspid aortic valve is worthy of special note, since it adds emphasis to the well-established fact,^{2,17,25} that antecedent injuries (*e. g.*, rheumatic) or congenital abnormalities of the heart valves are almost a *sine qua non* in subacute bacterial endocarditis, regardless of the nature of the infecting agent.

The total duration of the illness, which lasted approximately 5 months, is of some interest in the light of the suggestion by Craven, *et al.*,⁴ that endocarditis due to *H. influenzae* may be more acute than that due to *H. para-influenzae*, and that the non-hemolytic varieties of the 2 species produce more rapidly progressive endocardial infections than do their hemolytic relatives. It would seem from this case, in which the course was typically subacute, that until further evidence has been gathered the classification of influenzal endocarditis must remain strictly a bacteriologic one, since thus far no striking differences have been observed between true influenzal infection on the one hand, and para-influenzal infection on the other.

Summary. 1. A fatal case of subacute bacterial endocarditis caused by *Hemophilus influenzae*, Type a, with implantation on a

bicuspid aortic valve, is reported. This is apparently the first case record of proved endocardial infection with this organism.

2. The clinical course and pathologic findings in this case do not differ significantly from those previously described in *II. parainfluenzæ* endocarditis.

3. A brief period of chemotherapy with sulfanilamide failed to affect the outcome of the disease.

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CRITICAL RATES IN VENTRICULAR CONDUCTION.

UNSTABLE BUNDLE BRANCH BLOCK.

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CONDUCTION in the ventricles of a normal heart as expressed by the *QRS* complex of the electrocardiogram is a stable phenomenon. During the 40- to 50-year span of adult life this function is remarkably constant in the absence of heart disease, the *QRS* varying little if at all. Even considerable increases in rate of the normal heart fail to alter significantly the contour of this complex.

Several factors are believed to be concerned with this stability of function. One is the relatively smaller blood supply to the conduction tissue, which is said to be one-half that to heart muscle fiber.²² A second is the resistance of this tissue to anoxemia,^{6,12,21} and a third

factor is vagal control.^{7,15,20,23} All these and other factors, such as nervous chemical; and mechanical influences,⁵ need clarification.

Impairment of the circulation to the bundle of His and its branches is a fairly common occurrence in the course of disease of the coronary arteries. Often an expression of this condition is block in a branch of the bundle. Some idea of its frequency can be obtained from the observation by King⁹ that at the Johns Hopkins Hospital bundle branch block was seen more often than rheumatic fever. In a period of 5 years it was one-quarter as common as auricular fibrillation, three times as common as auricular-ventricular block, and four times as common as auricular flutter.

The usual type of bundle branch block is permanent, even though this be over a period of many years.

Bundle branch block may be transient. This type was first described by Lewis^{12a} in 1913. It has been reported many times since and is not rare. As in the case reported by Lewis, what usually occurs is that a patient who has developed bundle branch block, improves and eventually normal ventricular conduction is restored. Here there has been only one continuous episode of block.

Another form of transient bundle branch block has been described (Hermann and Ashman⁵), wherein many fluctuations back and forth between normal conduction and block take place. Responsible for these vacillations are several causes including changes in rate. The following report is concerned with this type of transient bundle branch block with frequent fluctuations between good conduction and block due to variations in rate. The changes are almost always complete within the duration of a single cycle, one *QRS* being normal and the next being that of bundle branch block, or the reverse. At a certain cardiac rate the equilibrium between normal ventricular conduction and block is so delicate that it is frequently disturbed and several changes back and forth may take place within the period of a minute or two. These changes are caused by such slight alterations as an increase or decrease in the heart rate of only one or two beats per minute. There is then a critical rate at which the appearance or disappearance of bundle branch block can be brought about by these very slight alterations in rate. Two such cases are described below, one in which the increase in rate of one beat or more per minute induced bundle branch block from normal ventricular conduction; the other in which a decrease in heart rate of one beat or more per minute acted similarly when the ventricle was beating at a certain rate.

Case Abstracts. CASE 1.—P.Y., admitted to the hospital (service of the late Dr. M. A. Rothschild) Dec. 12, 1930, was Russian, 49 years old and had 4 children. There was no history of any disease in childhood; she did not recall having had rheumatic fever or chorea. Venereal disease was denied. Symptoms of the menopause started in 1926. The present illness had its onset at about that time. She complained of spells of dizziness, buzzing

in the head, spots before her eyes, and a consciousness of her heart beat associated with some precordial pain. She was told her blood pressure was 170. After a short hospitalization she returned home and was able to perform most of her household duties. She did so for the next 4 years until 6 weeks before her admission to this hospital when she had an attack of pain over the precordium and with this a return of all the previous symptoms. The pain was moderately severe and radiated from the lower end of the sternum up to the throat. It lasted about 1 hour. Similar attacks of shorter duration occurred about 5 to 6 times daily and were usually brought on by effort. In this 6-week period she noticed very frequently during the day a peculiar, sudden, and momentary tinkling sensation inside her chest in the region of the left breast.

On examination, the patient did not appear ill and was quite comfortable lying in bed. Her temperature was 99.6° F., pulse rate 102, and respirations were 24 per minute. There was no dyspnea, orthopnea or cyanosis. The retinal vessels were thinned. The heart was not enlarged on Roentgen examination. When the patient was in the recumbent position the heart

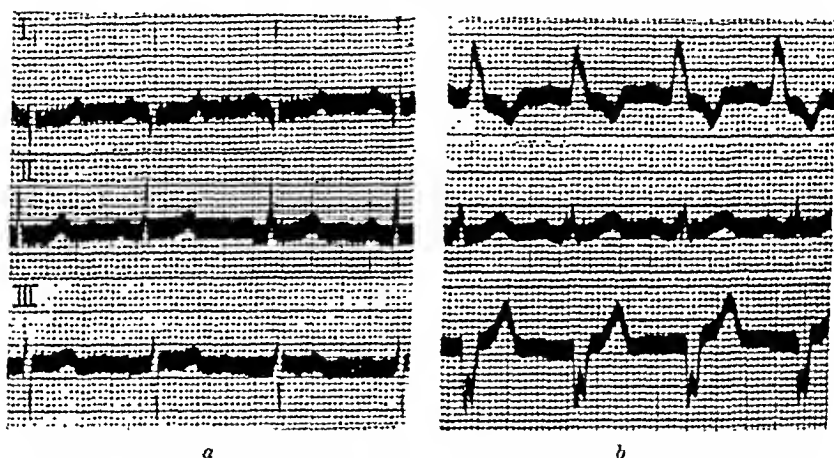


FIG. 1.—Case 1. Leads I, II, and III. (a) The patient in recumbent position: heart rate, 67 to 71 per minute; QRS, normal. (b) The patient standing; heart rate, 79 to 87 per minute; bundle branch block.

sounds were normal. The blood pressure was 180/100. The lungs were clear. The liver edge was palpable 3 fingers below the costal margin. There was slight bilateral pretibial pitting edema. The routine examination of the urine, complete blood count, and blood non-protein nitrogen were within normal. The electrocardiogram taken in the recumbent position was within normal except possibly for the Q wave in Lead I (Fig. 1a).

Clinical Diagnosis. Hypertensive and arteriosclerotic heart disease, coronary sclerosis, coronary occlusion(?), myocardial fibrosis, angina pectoris.

The patient remained in the hospital 2½ weeks. After the first few days she became very uncoöperative. She left the hospital against advice, her condition little changed.

Observations. With the patient sitting up in bed and connected to Lead I of the electrocardiograph, the string shadow was seen to perform short runs of two different types of excursions which alternated frequently, paroxysms of each lasting from several beats to several minutes. From a knowledge of previously taken records, it was readily apparent that the complexes, consisting of quicker and shorter QRS excursions and an upright T wave,

were those of normal conduction, and that the slower excursions of longer duration with the *T* wave directed downward were those of bundle branch block.

While the patient remained in the recumbent position the ventricular conduction was normal, the *QRS* being of the normal variety (Fig. 1*a*). While the patient was standing, the *QRS* waves were all of the bundle branch block type (Fig. 1*b*). When the patient was sitting, frequent fluctuations between the two types of *QRS* were observed with paroxysms of each of varying length.

Other maneuvers were carried out and their effect on the *QRS* observed. These were: inspiration and expiration with the patient recumbent, sitting, and also standing, exercise, carotid sinus pressure, and injections of atropine and pilocarpin.

Many changes back and forth between normal ventricular conduction and bundle branch block were recorded. When the rate was measured, it was seen that there was a close relationship between the ventricular conduction and cardiac rate. At slower rates ventricular conduction was normal; at faster rates bundle branch block was present. This was so, regardless of postural changes, respiratory variations and other maneuvers except insofar as they affected the rate of the heart.

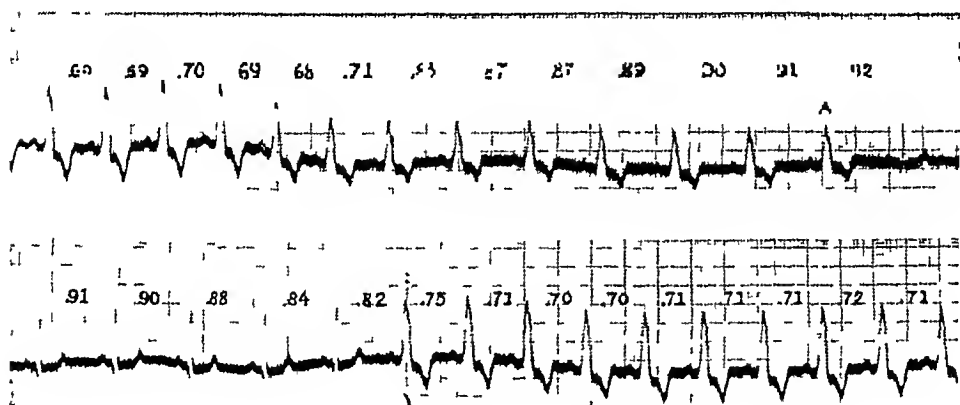


FIG. 2.—Case 1. Lead I. Arabic numbers are the *R-R* intervals in seconds. The patient in recumbent position after exercise. As the cardiac rate slows bundle branch block reverts to normal, after complex A, when the *R-R* interval increases from .91 to .92 second. At B there is a return to bundle branch block as the cardiac rate increases and the *R-R* interval is reduced from .84 to .82 second.

With the patient in the recumbent position following exercise, the ECG was recorded as the cardiac rate gradually slowed (Fig. 2). *R-R* intervals gradually increased from 0.68 to 0.91 sec. up to complex A. During 37 such cycles each *QRS* was of the bundle branch block type. As the slowing continued the next *R-R* interval was 0.92 sec., an increase of 1/100 sec. The *QRS* suddenly became normal and remained so during 7 beats while the *R-R* intervals ranged between 0.92 and 0.84 sec. The rate again grew faster. As the *R-R* interval decreased from 0.84 to 0.82 sec. there was a sudden change to bundle branch block (B) which persisted during the next 16 complexes with the *R-R* intervals between 0.82 and 0.68 sec. Thus before the first change, (A) bundle branch block was present at all rates faster than 65 beats per minute and after the second change (B) at all rates faster than 71 per minute. The change from block to normal conduction was sudden and complete within the period of one cycle. Though the transition was not gradual, there were some variations in the *QRS* and *T* complexes, readily seen 8 cycles before the change to normal conduction.

At other times the critical cardiac rate was observed to be 72, 73, 75 and 76 beats per minute, with bundle branch block when these rates were exceeded.

Four changes between conduction and block with variations of rate are illustrated in Figure 3.

The heart sounds at the apex were listened to by one observer* while another was watching the string shadow on the camera face. During normal ventricular conduction the first sound at the apex was clear, of medium pitch, moderately loud and not accompanied by a murmur. When bundle branch block was present the first sound was impure, much lower in pitch and intensity, and was immediately followed by a low-pitched, rumbling, systolic murmur lasting through one-half of systole. These sounds were observed many times. Each was always found true to one type of ventricular conduction and was regularly associated with it.

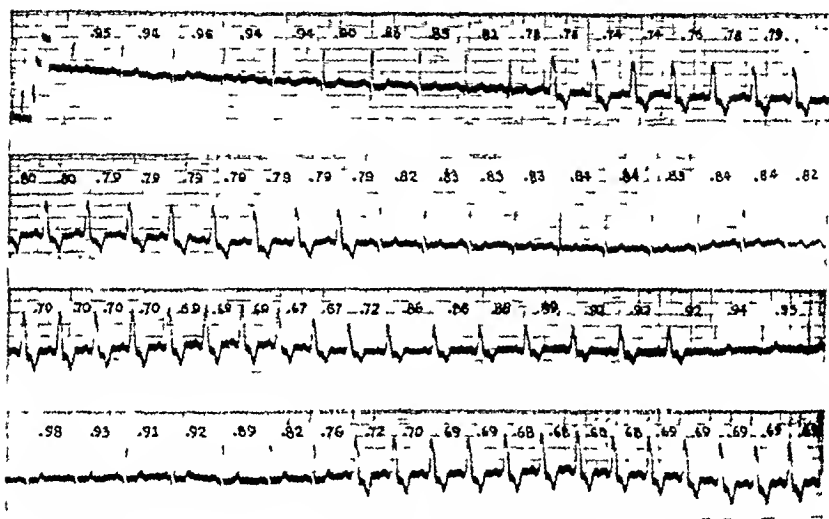


FIG. 3.—Case 1. Lead I. Four changes in conduction occurring during variations in cardiac rate are illustrated.

Frequently at the instant of change in conduction as noted by the change in heart sounds or motion of the string shadow of the electrocardiogram, the patient said she felt a sudden "tinkling" sensation in her chest.

The blood pressure was taken while the patient was in the sitting position when changes in the type of ventricular conduction were occurring. The blood pressure remained the same during normal conduction, during block, and during the transitions.

CASE 2.—E.B., admitted to the Beth Israel Hospital (service of Dr. I. W. Held) on April 15, 1940, was 50 years old, married, and had 2 children. Eight years ago she received treatment in the hospital for mild hyperthyroidism. The basal metabolic rate was +32.

The present admission to the hospital was due to an attack of an upper respiratory infection with fever, sore throat, cough, and pains in the arms and legs. On examination the temperature was 103.2° F.; pulse 64, and the respiratory rate 28. She appeared to be acutely ill. The pharynx was reddened. Neck veins were full. The lungs were clear. The heart was

* With the assistance of Dr. David Ball.

enlarged to the left. The cardiac rate was completely irregular but without a pulse deficit. A loud harsh systolic murmur heard at the apex was transmitted well to the axilla. P_2 was louder than A_2 and was accentuated. The blood pressure registered 124/58. Venous pressure was 18 cm. of water by direct measurement in an antecubital vein. The liver could not be definitely palpated. There was no edema, cyanosis or clubbing. Retinal arteries were narrowed.

Clinical Diagnosis. Acute upper respiratory infection. Arteriosclerotic heart disease, coronary sclerosis, myocardial fibrosis, auricular fibrillation, Class IV (new classification*). There was a moderate leukocytosis; 18,000, 69% neutrophils; a slight anemia, 4 million red blood cells and 70% hemoglobin. Erythrocyte sedimentation rate was 25 mm. in 45 minutes. The

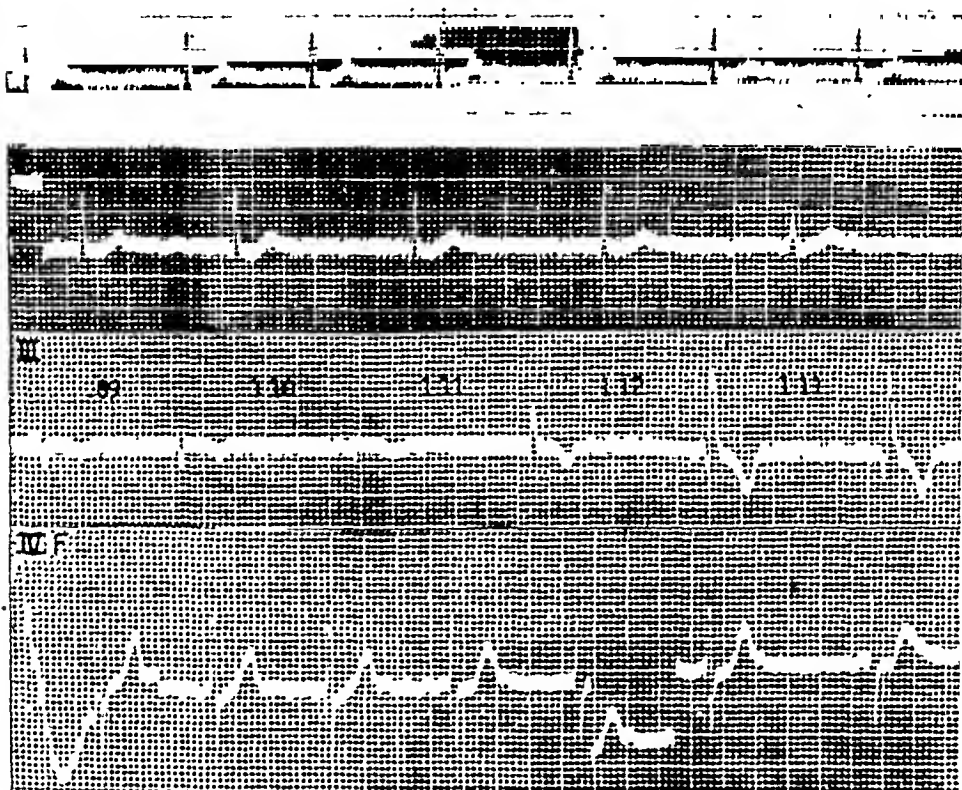


FIG. 4.—Case 2. Leads I, II, III, and IV F. The change to bundle branch block is seen in Lead III.

urine had a specific gravity of 1.020, and a slight amount of albumin. Non-protein nitrogen in the blood was 40 mg. per 100 cc. The blood culture was sterile.

The Roentgenogram revealed some general enlargement of the heart with local accentuation of the left auricular, left ventricular and right contours, also some calcification of the aortic arch and marked pulmonary hypervascularization.

The Roentgen-kymogram (Dr. I. S. Hirsch) indicated diminished amplitude of the aortic pulse wave, thought to be due to arteriosclerosis.

A four-lead electrocardiogram was taken on the day after admission (Fig. 4). There was auricular fibrillation. RT in Leads I, II, and IV F

* Nomenclature and Criteria for Diagnosis of Diseases of the Heart, 4th ed., New York Heart Assn., 1939.

were depressed. In Lead III the cardiac rate slowed and there occurred one transition to bundle branch block. Here there was at least one intermediary complex of lesser block indicating a more gradual transition to apparently complete block.

An electrocardiogram taken the next day (Fig. 5) revealed 22 changes back and forth between *QRS* waves of normal duration and those of some bundle branch block in 83 complexes recorded. There were 36 normal and 47 of incomplete bundle branch block.* The longest *R-R* interval which was followed by a normal *QRS* was 1.48 sec., equivalent to a rate of 40.4 beats per minute. All beats at faster rates had normal *QRS* complexes. The shortest *R-R* interval giving rise to bundle branch block was 1.49 sec., equivalent to a cardiac rate of 40.3 per minute, and here the *QRS* complex was that of lesser degree of bundle branch block.

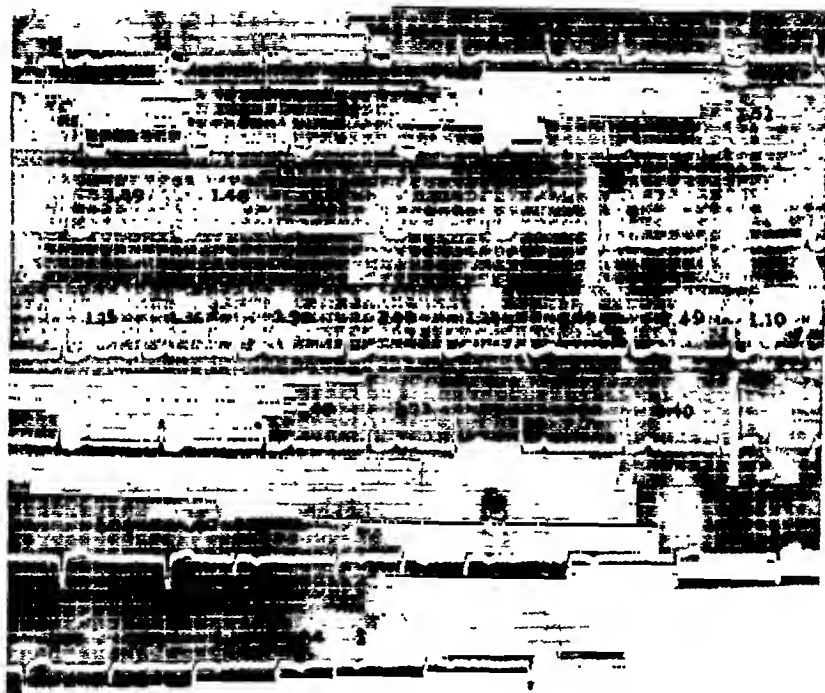


FIG. 5.—Case 2. Leads I, II, and III. Aberrant *QRS* forms lack the small initial deflection, are wider and slurred; the *R-T* segment is displaced. The *QRS* intervals vary from 0.07 sec. in the normal type to 0.12 sec. in some of the aberrant forms.

Discussion. The above 2 cases represent conditions of unstable conduction in the branches of the bundle of His. Frequently the equilibrium between normal and abnormal conduction became so delicate that it was disturbed by such subtle alterations as a change in the cardiac rate of only one beat or at times of even a fraction of a beat per minute. This delicate equilibrium was present when the heart was beating at a certain rate level. At this critical rate an

* The belief that these alterations in the *QRS-T* complex are due to a disturbance in the left (or right) bundle branch or their primary branches is assumed, rather than that they are produced by effects upon the more distal Purkinje system. This, however, is immaterial to the matter under discussion.

increase in the cardiac rate of only one beat per minute in Case 1, and, in Case 2 where the rate was quite slow, a decrease in rate of one beat per minute, was sufficient to block conduction in a bundle branch. The critical rate varied on different days. At different times in Case 1 it was 65, 71, 72, and 75 with block as these rates were exceeded. In Case 2 a record indicated that when the rate was 40.4 per minute or faster the conduction was normal and when the rate was 40.26 per minute or slower there was block.

The change from the normal to block or the reverse usually took place within the period of one heart cycle. Occasionally, however, the change to block was more gradual with at least one or two intermediary complexes of lesser block simulating the Wenckebach type. This type of bundle branch block with transitional complexes has been produced experimentally by varying the pressure with the blunt edge of a knife on the bundle or main branch.^{18,19} Its existence in human cases, however, is rare. An explanation given for this rarity is that the difference between normal conduction and complete bundle branch block is usually only from .04 second to .05 second, leaving little room for transitional stages of partial bundle branch block.²¹ In the 2 cases described above the small, gradual variations in rate occurring at times were adequate to bring out these transitional forms.

Digitalis was not taken by either patient up to the time of the observations described.

The pathologic anatomy of the unstable state of conduction may be of any type which involves the branches of the bundle of His or the bundle itself. Congenital septal defects, rheumatic syphilitic or other types of inflammatory diseases, and primary vascular changes, either acute or chronic, involving the arteries to the bundle and its main divisions, are possible causes. Vascular disease is the most common etiologic factor and was considered the cause in the 2 cases described above. The lesion may be a small local one catching a main bundle branch or it may be diffuse myocardial damage with diffuse involvement of the bundle branch system, as found in the majority of cases of chronic bundle branch block by Master and his associates.¹³ The second patient who had moderate enlargement of the heart and cardiac failure was most likely one of the diffuse type. The first patient had neither enlargement nor much failure so that one could be less certain of the extent of myocardial involvement.

The nature of the state of unstable conduction has been pictured by Carter and Dieuaide² who, in referring to conduction in the auricular ventricular bundle, stated: "... a few intact fibers may under favorable circumstances serve to carry on the process normally, while some subtle local circulatory deficiency or a temporary increase in vagal action may result in failure of the few remaining fibers to function."

Repair of the bundles of His when once destroyed probably does not occur (Erlanger).^{12b} Any recovery of function therefore is due

to physiologic alterations. Conduction in the bundle branches may be influenced by oxygen,¹ glucose,¹⁴ drugs such as digitalis,⁴ quinine¹¹ and morphine,³ and by changes in the cardiac rate.^{3,5,8,21,23} Temporary failure of conduction as in the above 2 cases is considered to be due to local functional changes which are the result of fatigue as described by G. C. Robinson.^{17a,b}

Unstable bundle branch block would be observed more frequently if at least one lead of the electrocardiogram were taken both in the recumbent position and after the rate has been increased by any measures deemed feasible, such as change in position or exercise. This would apply, of course, particularly to patients in whom disease of the coronary arteries is suspected. The first patient described in this report was referred to the hospital for study because repeated changes in the *QRS* complex were noted in the electrocardiogram taken in the office of the physician (the late Dr. M. A. Rothschild). The patient was in the sitting position. It is likely that, had the electrocardiogram been taken with the patient in the recumbent position when the heart rate was continuously below the critical level, it would have been normal, as was demonstrated later when the patient was in the hospital. Thus, an important aid in the evaluation of the case would have been missed, at least for some time. Doubtless the same situation holds for other cases. In patients with slow cardiac rates, as in Case 2, it would be desirable to take part of the ECG with the patient in the recumbent position after a period of rest, when slower rates obtain. An occasional instance of bundle branch block may be noted during a spontaneous paroxysm of sinus or auricular tachycardia or after auricular premature contractions.¹⁰

Of interest also is the fact that a symptom may be present at the time of change from one type of conduction to the other. A "tinkling" sensation in the chest was described by the first patient. This was noted several times to coincide with the changes in conduction as observed on watching the movement of the electrocardiographic string shadow. No unusual sensation in the chest was felt by the second patient.

The prognosis and treatment of unstable bundle branch block is essentially that of the underlying disease of the heart. With improvement the bundle branch block may disappear and normal conduction return permanently or for a long time. This occurred in the second case. If the damage to the myocardium is progressive, then permanent block would be expected. Progressive involvement of the right and left bundle branches might produce complete auriculoventricular block.²⁴

Summary and Conclusions. A state of unstable conduction in the branches of the bundle of His occurs which is closely related to the cardiac rate. A slight change in rate causes a bundle branch block when the heart is beating at a critical rate level. Bundle branch block similarly reverts to normal with slight changes in rate.

Transitions from normal conduction to bundle branch block and the reverse are usually sudden and take place within a single beat. Intermediary stages of lesser block are present at times.

The pathologic anatomy and mechanism of unstable bundle branch block are discussed briefly. Functional changes of fatigue or recovery from fatigue are probably responsible for the fluctuations between conduction and block.

Two cases are described. In one, ventricular conduction, as expressed by the *QRS*, appeared normal when the cardiac rate was below a critical level. Block was present when the rate was faster. In the second case, ventricular conduction was normal when the rate was above a critical level of 40.3 per minute, and block in a bundle branch was present when the rate was slower.

It is advisable at times, when myocardial changes are suspected, to take the ECG at more than one cardiac rate.

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SUBACUTE BACTERIAL ENDOCARDITIS ON THE RIGHT VENTRICULAR WALL OPPOSITE A VENTRICULAR SEPTUM DEFECT.

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DISCUSSING defects of the interventricular septum (*maladie de Roger*), Maude Abbott says: "... The clinical picture is thus that of absence of symptoms in the presence of distinctive physical signs

in an otherwise normal individual, and the significance of this lesion lies not in the functional effect of the defect, but in the great frequency with which a subacute bacterial endocarditis develops along its margins or on the opposite wall of the right ventricle. . . ."

A rather exhaustive review of the literature revealed an amazing sparsity of cases similar to the one which we are now reporting. We were able to find but 4 such cases, all in older patients than ours. This is also the only case in which the valve leaflets and the chordæ



A

were not as yet involved by the endocarditis.^{1a 2 3} In a personal communication Maude Abbott^{1b} wrote "... this is a clear cut example of an infective endocarditis of the wall of the right ventricle opposite a localized defect of the interventricular septum without vegetations elsewhere. It supplies proof of the direction of the current from the left to the right through the defect."

Report of Case. J. P., 7-year-old white Italian male child, the fifth of 6 children—all of whom are living and perfectly well. There is no history

of the occurrence of any congenital defect nor of any cardiac lesions in the family as far back as the grandparents. Physical examinations of the parents and siblings were not made. The patient developed normally up to the time of the present illness. He was in the third grade of the public school. His tonsils and adenoids were removed at 6 years due to frequent



B

FIG. 1.—*A*, The opened right ventricle showing the inter-ventricular defect as well as the localized patch of endocarditis on the opposite wall (round area just beyond end of rod). Petechial hemorrhages in the myocardium are also readily seen. *B*, More detailed view of defect.

attacks of tonsillitis. His congenital heart-lesion was first noted at 4 months. However, he was entirely symptom-free up to the onset of his present illness.

His illness began on June 17, 1939, and was characterized by malaise, anorexia and slight fever (up to 101.4° F.) followed by drowsiness. On June 20th physical examination revealed an apathetic, listless and obviously

sick child. The temperature was 100.2°, his pulse was 140 and of fair quality. His respirations were regular, not labored and about 30 per minute. There was no cyanosis. Both turbinates were boggy and red and the nares were filled with a somewhat gelatinous mucoid secretion. The throat was only slightly reddened. The teeth were markedly carious. The anterior and posterior cervical lymph nodes were palpably enlarged. His chest had a normal contour, and his lungs were resonant throughout. The heart was enlarged to the left and presented a systolic thrill, felt over the entire precordium, and most marked at the base. A loud continuous to and fro murmur, heard over the entire precordium, was most distinct at the apex, and could also be heard in the neck vessels as well as in the left posterior chest. The spleen was markedly enlarged, extending almost to the level of the iliac crest. The liver was also enlarged, extending to about 2 fingers below the costal margin. No other masses or viscera could be felt. There was no edema of the extremities. Urinalysis was entirely negative. That night his temperature rose to 104.4°. He became somewhat delirious. The following afternoon several scattered areas of ecchymosis were found over the thighs and lower abdomen (these were between 2 and 3 inches in diameter). No petechiæ could be found. A tentative diagnosis of subacute bacterial endocarditis was made. He was admitted to this hospital on June 23. His temperature continued septic (105.6° to 100.2° F.). On June 25, he became somewhat jaundiced. On June 27 the blood culture was positive for streptococcus (alpha). He continued downhill, despite 3 small (160 cc.) transfusions and sulfanilamide treatment. Roentgen rays on June 24, and again on June 26, showed no pulmonary lesions. Repeated urinalyses failed to reveal red blood cells until on July 9 an occasional red cell was noted. There was a slight trace of albumin and occasional white blood cell. Blood counts showed Hgb. from 65% to 50%; red blood cells from 3,270,000 to 2,420,000. White blood cells varied from 18,350 (June 24) to 3,100 (July 1); neutrophils from 80% (June 24) to 95% (July 3). Blood culture was positive on several occasions for alpha streptococcus. The various agglutination tests (typhoid, para-A, and B, *B. abortus*, *B. melitensis*) were all negative. The blood Wassermann test was negative. Blood smear (July 3) showed no abnormal leukocytes, but a marked shift to the left. Red cells show a moderate variation in size and shape; no nucleated reds. Electrocardiogram: moderate left axis deviation, the QRS complex of the "M" shape variety, with some thickening and slurring of all the limbs (indicating intraventricular conduction defect). Fluoroscope and Roentgen ray films of the heart showed it to be moderately enlarged, and of the "wooden shoe" shaped type. Petechiæ were first noted on July 4; 2 were under the conjunctiva of the left eye. July 5, several additional petechiæ appeared over the body. He continued rapidly downhill and died July 9, 1939.

Autopsy (12 hours postmortem): The arteries showed no atheroma or arteritis. There was no dilatation or hyperplasia of either the pulmonary artery or the aorta. The pulmonary artery was 3 cm. in circumference; the aorta 4½ cm. There was no evidence of collateral circulation. The coronary arteries and veins were normal. The heart was normal in its position. It was moderately hypertrophied in both the right and left sides. It weighed 120 gm. The right auricle measured 3 by 5 cm. and its wall was 1 mm. in thickness; right ventricle was 5 by 6 cm. and its wall was 2 mm. in thickness; left auricle 3 by 4½ cm. and its wall was slightly more than 1 mm. in thickness; left ventricle 5 by 5½ cm. and its wall was 8 mm. thick. The valve rings were moderately enlarged. The mitral valve measured 5.6 cm. and the tricuspid valve 7.8 cm. in circumference. There were no anomalies or vegetations of any of the valve leaflets. The myocardium showed numerous petechial hemorrhages. The interventricular septum had

a smooth punched-out defect in its membranous portion 1 cm. in diameter. This was surrounded by a thick fibrous ring. On the wall of the right ventricle opposite this defect there was a fan-shaped area of endocarditis, 3 cm. by 2 cm. in diameter. This area was covered with about 100 small warty vegetations which were slightly friable but seemed to contain considerable fibrous tissue. Sections from these vegetations showed them to be composed of an amorphous mass of fibrin and blood platelets. In the deeper portions of the vegetations there was beginning organization with fibroblasts, newly-formed blood-vessels and an infiltration of inflammatory cells, mostly neutrophils. Only 1 group of streptococci could be found in these vegetations. There was a complete erosion of the endocardium in these areas.

Comment. The endocardium against which an abnormal flow of blood was directed was evidently damaged. This damage favored the implantation of bacteria from the blood stream resulting in the production of a localized endocarditis. The portal of entry of the blood stream infection may very likely have been the carious teeth.

Summary. A report is submitted of a case of Roger's disease with subacute bacterial endocarditis. This was localized to an area in the right ventricle opposite the interventricular defect and was apparently caused by the force of the bloodflow, resulting from arterio-venous shunt. This case appears to be unique in medical literature.

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THE INTRACRANIAL AND PERIPHERAL VASCULAR EFFECTS OF NICOTINIC ACID.*

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ONE of the conspicuous effects of nicotinic acid† is flushing of the skin. Abramson, Katzenstein, and Senior¹ have demonstrated by means of plethysmographic and skin temperature studies that an

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† Monoethanolamine Nicotinate (Abbott).

increase in bloodflow through the arm, and to a lesser extent through the leg, results from the oral and intravenous administration of nicotinic acid. That an associated dilatation of the cerebral vessels might also occur has led to the hope that the drug might have a usefulness in certain diseases of the brain by increasing the blood supply to the areas involved. Direct evidence that cerebral vasodilatation follows the administration of nicotinic acid has been offered by Moore,³ who observed an increase in the diameter of the pial vessels in cats. In a few instances in which lumbar puncture was done, this author also noted a rise in spinal fluid pressure during the appearance of the vasodilatation of the skin. Moore reported improvement of subjective and objective symptoms in 5 cases of multiple sclerosis which he treated with nicotinic acid. He concluded that the favorable results seen following such treatment might be in part due to the effect of the increased bloodflow in the brain.

The present study was carried out to compare by indirect evidence the relative vascular effects of nicotinic acid on the brain and the arm. Several passive and coöperative dementia præcox patients were utilized for this study. The nicotinic acid was injected in doses varying from 12.5 to 150 mg. into the basilic vein, the carotid artery, or the brachial artery.

Peripheral Vascular Effects. Flushing of the skin beginning in the face and spreading to the neck, chest, abdomen, arms and back occurs within 1 to 2 minutes, reaching its height within several minutes following the intravenous injection of nicotinic acid in doses from 25 to 150 mg. With the larger doses the flushing is very marked. Rarely is it discernible to any degree below the abdomen. When flushing of the face is marked, injection of the conjunctival vessels is sometimes present. Stroking of the flushed skin of the chest or back with the finger-nail produces a red line followed immediately by a white line which lasts for several minutes. Flushing of the skin following intravenous administration of the larger doses disappears within about $\frac{1}{2}$ hour. The blood pressure shows either an insignificant or a slight rise (up to 10 mm. systolic). In one instance following the intrabrachial injection of 100 mg., the blood pressure rose from 140/100 to 180/110, returning to its original level within 7 minutes. The change in pulse rate was either insignificant or slight, in no instance increasing beyond 12 beats per minute.

When the nicotinic acid is injected into the brachial artery in doses varying from 12.5 to 100 mg., flushing of the injected arm occurs within 1 or 2 minutes and is followed quickly, with the larger doses, by flushing of the face and other parts. The skin of the injected arm shows more flushing and is warmer to the touch than that of the opposite arm. With the smaller doses, the flushing may be confined practically entirely to the injected arm. When the drug is injected in doses of from 25 to 150 mg. into the carotid artery,

marked flushing of the face occurs almost immediately, and is soon followed by flushing of the parts usually involved following intravenous administration.

Intracranial Vascular Effects. 1. *Effect on the Retinal Vessels.* In no instance following either the smaller or larger dose of nicotinic acid was vasodilatation or vasoconstriction of the retinal vessels observed by ophthalmologic examination.

2. *Cerebrospinal Fluid Pressure.* This was measured in 8 cases, in 6 cases following intravenous injection of 100 mg., and in the other 2 following intravenous injection of 150 mg. There was no significant change in the cerebrospinal fluid pressure either during or for some time after the height of the flushing of the face, which was very marked in all cases. In one instance, in order to discover whether the cerebral vessels respond differently when narcosis is first induced, 1 subject was given 0.75 gm. of sodium amytal by vein. During the resulting deep narcosis, 150 mg. of nicotinic acid was administered by vein. Very marked flushing of the skin occurred. The cerebrospinal fluid pressure, measured for 30 minutes, showed a rise of only 20 mm. of water.

3. *Arterio-jugular and Arterio-basilar Differences in Oxygen Content.* These were compared following intravenous administration of 100 to 150 mg. of nicotinic acid in 4 cases, and in 5 cases following intracarotid administration of 50 to 150 mg. In 5 other cases the oxygen "uptake" of the arm alone was measured following intrabrachial administration of 25 mg. of the drug.

Results. (a) Following intravenous administration of the drug, there was a significant diminished arterio-jugular difference in oxygen content in 1 subject. By contrast, a moderate to marked diminished arterio-basilar difference in oxygen content occurred in 3 of the 4 subjects (Table 1).

TABLE 1.—ARTERIO-JUGULAR (A-J) AND ARTERIO-BASILIC (A-B) DIFFERENCES IN OXYGEN CONTENT (VOL. %) FOLLOWING INTRAVENOUS ADMINISTRATION OF MONOETHANOLAMINE NICOTINATE.

Experiment No.	Dose (mg.).	Before injection.		Height of reaction.	
		A-J.	A-B.	A-J.	A-B.
1	100	8.0	7.4	7.2	2.5
2	100	7.3	7.2	10.5	8.7
3	150	5.3	7.3	4.3	2.3
4	150	9.2	5.3	6.0	2.9

(b) Following intracarotid administration of the drug, no significant change in arterio-jugular difference in oxygen content resulted. In 3 of the 5 instances, however, a moderate to marked diminution in oxygen "uptake" by the arm occurred (Table 2).

(c) Following intrabrachial administration of the drug with doses much smaller than those injected into the carotid artery, a very marked diminution in arterio-basilar difference in oxygen content occurred in all 5 subjects (Table 3). Samples of arterial and basilar

blood taken simultaneously from the uninjected arm of 2 of the subjects showed no change in oxygen "uptake."

TABLE 2 —ARTERIO-JUGULAR (A-J) AND ARTERIO-BASILIC (A-B) DIFFERENCES IN OXYGEN CONTENT (VOL %) FOLLOWING INTRACAROTID ADMINISTRATION OF MONOETHANOLAMINE NICOTINATE.

Experiment No	Dose (mg.).	Before injection.		Height of reaction	
		A-J	A-B.	A-J.	A-B
5	50	6 1	8 5	5 5	6 8
6	150	3 5	4 5	4 8	6 2
7	50	5 5	4 1	5 5	2 7
8	50	4 9	4 6	4 0	1 9
14	50	4 4	4 0	4 0	2 9

TABLE 3 —ARTERIO-BASILIC DIFFERENCES (A-B) IN OXYGEN CONTENT (VOL %) IN INJECTED AND UNINJECTED ARM FOLLOWING INTRABRACHIAL ADMINISTRATION OF MONOETHANOLAMINE NICOTINATE

Experiment No	Dose (mg.).	Injected arm		Uninjected arm	
		Before injection.	Height of reaction	Before injection	Height of reaction
9	25	8 2	1 0	8 4	8 4
10	25	7 5	1 5		
11	25	5 4	1 9	8 4	10 1
12	25	6 6	2 6		
13	50	8 9	1 7		

Effect of Nicotinic Acid on Artificially Produced Raynaud's Syndrome.

In previous experiments, Myerson, Loman, Rinkel and Lesses⁴ demonstrated that a Raynaud attack can be simulated following intrabrachial administration of epinephrine in very small concentrations (0.001 to 0.0001 mg.). With doses of 0.01 mg. of this drug a very severe attack is produced. The pallor of the arm and hand following the latter dose lasts about 15 minutes before it begins to wear off.

In 2 subjects such an attack was produced by injecting 0.01 mg. of epinephrine into the brachial artery. At the height of the reaction, which began about 2 minutes later, 25 and 50 mg. of nicotinic acid, respectively, was administered into the artery. Within $\frac{1}{2}$ to 1 minute the pallor began to be superseded by flushing occurring, first, in the forearm, then in the palm, and finally in the fingers. Within 10 minutes in the first case and within 15 minutes in the second, all the pallor had been replaced by flushing. In 2 other subjects nicotinic acid in doses of 25 and 50 mg. was given before the epinephrine (0.01 mg.), both drugs being given by intrabrachial route. Only slight pallor was produced in each subject, lasting about 5 minutes.

Contrast Between Nicotinic Acid and Some Parasympathomimetic Drugs. In previous work Myerson, Rinkel, Loman and Myerson² demonstrated that prostigmin has a powerful synergistic action with acetylcholine, particularly with acetyl-beta-methylcholine chloride, and that atropine completely blocks the action of the above two choline. Nicotinic acid, however, is not synergistic with prostigmin,

nor is it antagonized by atropine, at least in respect to vasodilatation. On the other hand, acetylcholine and acetyl-beta-methylcholine chloride are less effective in overcoming the Raynaud-like attack produced by epinephrine than is nicotinic acid.⁵

Discussion. That nicotinic acid is a relatively ineffective cerebral vasodilator appears to be indicated by the following: 1, it fails to influence the cerebrospinal fluid pressure; 2, it does not dilate the retinal vessels (comparable to the pial vessels); and 3, probably most significant, it changes only slightly the arterio-jugular difference in oxygen content.

The fact that the cerebrospinal fluid pressure does not change indicates either that the pial vessels do not alter in diameter, or that the cerebral venous pressure does not increase. It is possible, however, for the bloodflow in the intracerebral arterioles and capillaries to increase without pial vasodilatation or an increase in venous pressure, so that the spinal fluid pressure does not change. But under such conditions one should expect a diminished arterio-jugular difference in oxygen content. The fact that this occurs only occasionally, or in much less degree than that observed in the arm, strongly suggests the relative ineffectiveness of nicotinic acid as a cerebral vasodilator. This contrast of vascular effect in the brain and arm is particularly evident when the drug is administered by brachial and carotid routes.

Other drugs, such as histamine and acetylcholine, have been observed to produce dilatation of the pial vessels with a coincident rise in spinal fluid pressure. In our experience no significant or regular change in arterio-jugular difference in oxygen content occurs at the height of the reaction produced by these and other vasodilator drugs.² Thus, feeble dilatation of the intracerebral vessels may be associated with a relatively strong dilatation of the pial vessels.

The theory, that when the face flushes the brain flushes, is not borne out by these studies. It is more accurate to state that both areas probably do not flush to the same degree or that flushing of the face is not necessarily associated with flushing of the brain. The obvious resistance of the cerebral vessels to changes in bloodflow following the administration of nicotinic acid and other common vasodilator drugs suggests the probability that attempts to affect impaired cerebral neurons by such means will fail. Whether the physiologic demands of neurons damaged by disease processes can be supplied by increasing the cerebral bloodflow is in itself very questionable.

On the other hand, because of its marked peripheral vasodilating action, nicotinic acid may have a possible clinical usefulness in peripheral vascular conditions in which an increased bloodflow is desired. Such an application of the drug is suggested by the observation that a Raynaud attack, artificially produced, is shortened or overcome by the drug.

Summary. Nicotinic acid was administered by intravenous, intrabrachial and intraeartoid routes to a group of subjects for the purpose of comparing the cerebral and peripheral (arm) vascular effects. The following observations were made:

1. The cerebrospinal fluid pressure is insignificantly altered.
2. The caliber of the retinal vessels is unchanged.
3. The cerebral bloodflow, using changes in arterio-venous differences in oxygen content as an index, is only slightly increased, while the bloodflow in the arm is usually moderately to markedly increased. This difference in response in the two loci is particularly obvious when the drug is injected into the carotid and brachial arteries.

4. Nicotinic acid shortens the Raynaud-like response produced by epinephrine when both drugs are injected into the brachial artery. This peripheral action of the drug suggests a possible usefulness in Raynaud's and other peripheral vascular diseases.

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VASOMOTOR DISTURBANCES IN PERIPHERAL NEURITIS.*

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STUDIES of the cardiovascular manifestations of beri-beri have strongly suggested that the peripheral circulation in the extremities is definitely disturbed and that this disturbance may be an important factor leading to circulatory failure in the disease.^{2, 6, 7} Since peripheral neuritis is one of the common manifestations of beri-beri, there has been some speculation as to whether the disturbances in the peripheral circulation might be due to coexistent involvement of the sympathetic nervous system. Therefore, it was decided to study patients with peripheral neuritis due to dietary deficiency, but

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without circulatory failure, in order to determine if any abnormalities of sympathetic vasomotor function were present.

Methods. The skin-temperature of the pads of the digits was measured by thermal junctions lightly applied with adhesive tape. Body temperature was measured by a thermal junction inserted 5 cm. above the rectal sphincter. Room temperature was measured by a thermal junction suspended in the air of the room. The galvanometer allowed the detection of changes of 0.1°C .

The room was draught free, and was maintained at as constant a temperature as possible. Plethysmographic measurements of volume and pulse-wave changes in the fingers and toes were recorded optically by the method of Bolton, *et al.*¹ The subject lay lightly covered for 20 to 40 minutes while control observations were made. The body was then warmed with heating pads and blankets, and by immersing one arm to the elbow in water at 45°C . Temperature and plethysmographic measurements were repeated at frequent intervals. When full reflex vasodilatation had been obtained, stimuli were applied which are known to induce, through the mediation of the sympathetic nervous system,⁴ brief vasoconstriction in the digits. These stimuli were the following: (a) application of ice to the skin; (b) pricking with a pin a sensitive skin area; (c) startling the subject by making a sudden loud noise; directing the subject (d) to take a deep breath, or (e) to solve an arithmetical problem. The body was then cooled by removing the blankets and heating pads, and transferring the arm to cool water (20°C). Again temperature and plethysmographic measurements were taken at frequent intervals.

The patients (Table 1) were selected from the medical wards where their diet and vitamin intake were carefully regulated. Eight patients had "alcoholic" peripheral neuritis; one, peripheral neuritis of pregnancy; and one, peripheral neuritis following disulfanilamide poisoning. Thirty-five tests were carried out on these patients, some of whom were repeatedly tested over periods as long as 4 months. At the conclusion of each test a neurological examination was made.

Results. Half of the patients with peripheral neuritis involving the legs also had a disturbance of the sympathetic vasomotor activity in the feet (Table 1). With one exception these were all untreated patients who had tenderness, definite sensory defects, and areflexia in the legs. The circulatory abnormality consisted of decreased vasomotor tonus in the feet. The toes were constantly warmer than the fingers even with the body exposed in the cool room. After warming the body, the temperature of the toes rose slightly or remained unchanged, while the temperature of the fingers rose to or above that of the toes (Chart 1). At this time the plethysmographically recorded vasoconstrictions in response to brief vasoconstrictor stimuli were slight in the toes as compared with the fingers (Fig. 1). On cooling the body the temperature of the toes decreased slightly, while that of the fingers fell more rapidly and reached a lower level (Chart 1).

Both the digital temperature and the plethysmographically recorded volume changes indicated a decreased vasomotor tonus in the feet. In healthy persons we have always found a greater vasomotor tonus in the feet than in the hands. This confirms the

— AFTER TREATMENT.

[illegible]

observations of others.^{3,5} However, we have frequently found a decreased vasomotor tonus in the feet of patients subjected to lumbar

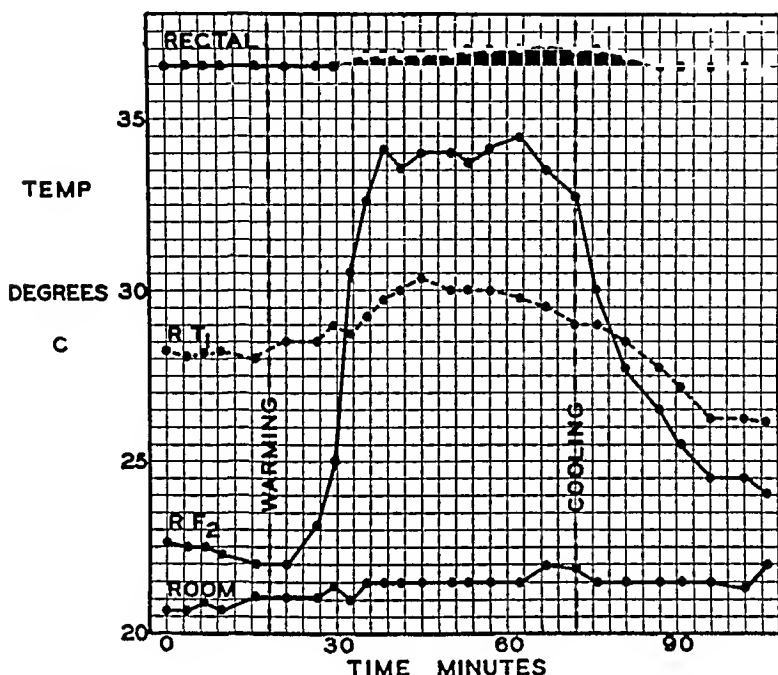


CHART 1.—Rectal temperature, the skin temperature of the right great toe (R T₁) and of the right forefinger (R F₂), and the room temperature, during a test of the effects of body warming and body cooling on a patient with "alcoholic" peripheral neuritis.

sympathectomy. Indeed, in our patients with peripheral neuritis the measurements of digital temperature and volume changes strongly resembled those found in persons in whom only a partial

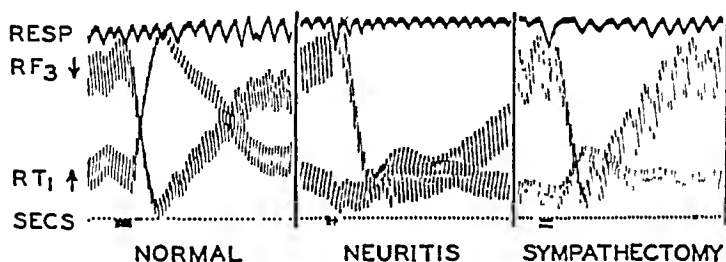


FIG. 1.—Plethysmographic records of vasoconstrictor responses in the right third finger (R F₃) and right great toe (R T₁) of a normal subject, a patient with "alcoholic" peripheral neuritis, and a patient subjected to bilateral lumbar sympathectomy. The arrow indicates the direction of decrease in volume of the digit. The top tracing shows respiration (Resp.) with the down stroke for inspiration. At the signal (below the seconds marks), ice was applied to the skin of the face.

sympathectomy of the feet had been secured by resection of the first and second lumbar sympathetic ganglia (Fig. 1).

One interesting phenomenon encountered in the involved toes was a delay in the vasoconstrictor response which appeared 7 to 10 seconds after the stimulus, instead of the normal 3 to 5 seconds (Fig. 1). This was found in 3 patients. We have never seen a response as much delayed in normal subjects, or in patients suffering from other diseases.

Three patients were placed on vitamin free (pellagra-producing) diets as soon as they were admitted to the hospital. On this regimen the polyneuritis failed to improve, and the vasomotor paresis became more complete. When thiamin chloride, 50 mg. daily, was administered parenterally, there was an improvement of the vasomotor disorder within 2 weeks, though there was not a return to normal. After this initial improvement, progress was slow and was not apparently accelerated by a diet rich in all vitamins.

The vasomotor disturbance seemed to improve more rapidly than the sensory-motor abnormalities with the exception of muscular tenderness. For example, 1 patient (I. F.) was retested after 2 months of high vitamin therapy at home. At this time the vasomotor responses had returned to normal. The sensory-motor signs, however, were unchanged. The fact that the vasomotor disorder seemed to improve faster after treatment than the sensory-motor disturbance may explain why the former was often not found in patients who had been treated for prolonged periods but still had sensory-motor signs.

One patient (F. M.), seen for the first time after prolonged dietary therapy, still had almost complete loss of sensation in the feet and lower legs. She had no vasomotor hypotonus in the feet. On the contrary, the feet and lower legs were blue and cold. On warming the body, the temperature of the toes rose promptly, and the plethysmographically recorded vasoconstrictor responses were normal except for a delay of the type mentioned above. The patient suffered from "trophic" ulcers on both third toes. For this reason, and against our advice, she was subjected to a unilateral lumbar sympathectomy. After the operation the sympathectomized foot became warm and pink, showing that the sympathetic nervous system had formerly been active. The ulcer, however, showed no greater tendency to heal on this side than on the opposite, cool, unsympathectomized side. This case demonstrates the fact that there was no correlation between the severity of the sensory loss and the vasomotor hypotonus.

That there was no correlation between the degree of motor weakness and the vasomotor disturbance is illustrated by the findings in the patient with polyneuritis of pregnancy. She had a most severe motor paralysis of the lower legs with only slight sensory defects. There was no more than a minimal vasomotor disturbance.

Two of the patients had "trophic" ulcers on the toes. These ulcers were observed in a patient with vasomotor hypotonus and warm feet, and in the patient, cited above, with cold feet. Both

patients had severe sensory loss. This suggests that the ulcerations were due to the sensory defect and not to the vasomotor disorder.

Discussion. The finding of a vasomotor disturbance in the feet of patients suffering from peripheral neuritis of the legs, associated with vitamin deficiency, was too frequent to be coincidental. The combination suggested that the vasomotor and sensory-motor abnormalities might have a common pathogenesis. Since the vasomotor disturbances resembled those found in partially sympathectomized limbs, the likely explanation is that these vasomotor disturbances are due to involvement of the sympathetic nerves, just as the sensory-motor signs are due to involvement of the sensory-motor nerves.

It would appear that part of the vasomotor disturbance in these patients was not due to an anatomic defect, since it subsided within 2 weeks of instituting therapy. However, the residual abnormality was either structural or, if functional, only slowly reversible, since a complete return to normal occurred either very slowly or not at all. The evidence indicates that during therapy the recovery was more rapid in the vasomotor than in the sensory-motor system.

One interesting vasomotor abnormality peculiar, so far as we know, to these cases was the much delayed vasoconstriction in the involved toes in response to appropriate stimulation. The reason for this delay is not apparent. We have not observed it in patients after partial or complete sympathectomy.

Summary. Disturbance of the vasomotor reactions in the feet was frequently found in untreated patients who had peripheral neuritis of the legs. The disturbance was characterized by a decrease in the vasomotor tonus of the feet, resembling that found after incomplete sympathectomy. A delayed response to vasoconstrictor stimuli was also found in the toes of some of the patients.

There was no rigid relationship between the degree of vasomotor disturbance and the loss of sensation or muscular power. In general, the more severe cases of peripheral neuritis were the ones with vasomotor abnormalities.

Definite improvement in the vasomotor disturbance occurred within 2 weeks of instituting appropriate treatment. However, a complete return to normal vasomotor function required a longer period of therapy.

This investigation was conducted with the technical assistance of Miss Sara B. Merritt, B.S. The authors are indebted to Dr. Alan Bernstein for granting permission to include in this paper observations on one of his patients.

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BLOOD AND URINE CHLORIDES IN 22 CASES WITH DIABETES INSIPIDUS.

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PATIENTS with diabetes insipidus drink large quantities of water and pass a great deal of urine, often amounting to 10 or more liters per day. If the polyuria of diabetes insipidus is regarded as a diuresis, and I believe that it may be, one would expect to find an increased excretion of sodium chloride in the urine and a decreased serum chloride level, for the reason that diuretics cause an increased excretion of salt along with the increased volume of urine. There are differences of opinion with regard to the serum chloride level and the chloride excretion in the urine in diabetes insipidus. Some investigators have reported hyperchloremia and hypochloremia, hyperchloruria and hypochloruria. Different results, too, have been reported on the effect of pituitrin on the serum and urine chlorides in this disease. Since such variable impressions have been based largely on rare cases, a study was made of the chloride content of the serum and urine in a group of 22 patients over a period of 5 years. In addition, it appeared of interest to determine whether pituitrin, an antidiuretic, would alter the chloride findings. This paper reports the results, which are consistent, of the total chlorides in the serum of 22 patients with diabetes insipidus and, in addition, the total sodium chloride excretion in 2 of these individuals.

There has been considerable interest in chlorides in relation to diabetes insipidus for many years. As far back as 1872, Neubauer and Vogel¹¹ found an increased chloride excretion in a patient with diabetes insipidus and on one day it reached the enormous amount of 29 gm. Oppenheim¹² obtained a total of 20 to 30 gm. of sodium chloride in the daily urine of 4 cases. There was a marked salt hunger and when the salt intake was reduced, the sodium chloride excretion was less, although the volume of urine was unchanged. The salt had no diuretic effect. More recently, however, it has been shown by Fitz,⁵ Rosenbloom and Price¹⁵ and Curtis¹ that the output of sodium chloride in diabetes insipidus was normal; but increasing the salt in the diet increased the total volume of urine in order to get rid of the excess salt. Curtis¹ also observed that under water restriction with salt feeding, the kidneys were able to concentrate both chlorides and solids. Swan¹⁷ suggested as the result of his experiments that the changes in water metabolism in diabetes insipidus are secondary to changes in chloride metabolism while Peters¹³ reported that small amounts of salt are swept out by the flow of water. On the other hand, because of the varying results that Veil²⁰ obtained with serum and urine chlorides in 4 cases, he

classified diabetes insipidus into the hyperchloremic-hypochloruric and the hypochloremic-hyperchloruric types.

Hyperchloremia in untreated diabetes insipidus has also been reported by Rabinowitch,¹⁴ Curtis,⁴ Butler and associates³ and by Talbot and associates.¹⁸ Some of these authors found that the blood chlorides decreased following pituitrin administration. That pituitrin stimulated and increased the total chloride excretion in the urine, while the diabetes insipidus was relieved has been observed by von den Velden,¹⁹ Williams,²³ Rabinowitch¹⁴ and by Butler, Harper and Carey.³

In contrast, there have been studies on this disease which indicated that the blood chloride concentration was normal or low and that the excretion of salt was not affected or was decreased by pituitrin administration. Blumgart,² Weir,²¹ White and Findley,²² and Winter, Ingram and Gross²⁴ observed normal blood or serum chloride levels which were not appreciably altered by pituitrin therapy. In addition, White and Findley²² and Smith and MacKay¹⁶ noted that pituitrin did not affect the total urine chloride excretion while Weir²¹ noted a distinct drop in it. Mainzer⁹ found a very low serum chloride in 4 cases of untreated diabetes insipidus and in 2 cases the serum chloride, determined again after pituitrin therapy, rose to normal.

Procedure. The patients studied were ambulatory and consisted of 15 males and 7 females who have had diabetes insipidus for a number of years. Their ages ranged from 12 to 67 years of age, although most of them were below 25 years. Their salt intake appeared to be that of the usual person and they had no craving for it. The diets were the same during the various tests. Most of the patients had a daily urine output of about 10 liters without treatment and a normal urine volume with sufficient pituitrin therapy. The urine examinations were normal.

The serum chloride was determined on one or more occasions in 22 patients without the administration of pituitrin. During these tests the fluids were taken as desired and usually ranged from 8 to 14 liters. In 15 of these patients, the pituitrin was omitted for from 3 to 10 days before the tests were made, whereas in 7 cases no pituitrin was taken for 2 months to several years previously. The serum chloride was tested again in 11 cases after the patients had pituitrin therapy for a period of time and when they were well controlled with the drug. Fluids were taken as desired and the amounts were within the normal range.

The total excretion of chlorides in the urine in 2 patients was determined daily for 36 and 18 days respectively in the hospital. They were on a constant house diet which contained about 200 gm. of carbohydrates, 90 gm. of fat and 90 gm. of protein. In the first case, the salt in the diet was calculated daily and sodium chloride was added to make the total sodium chloride intake exactly 10 gm. daily, while in the second case the salt intake was approximately 10 gm. daily. The urinary chloride is expressed as sodium chloride in the charts so that the excretion of salt may be compared more easily with its intake. The studies were made with and without pituitrin therapy and in addition, the serum chloride was determined daily or on alternate days.

Serum Chloride Results. The results of the serum chloride findings* (Tables 1 and 2) were consistent and did not show the variations recorded by observers already mentioned. The chloride concentrations in all of the cases came within the normal range, regardless of whether the patient had omitted pituitrin for only a few days or whether the patient had not been treated with pituitrin for several years and excreted gallons of urine daily during that period. However, in 2 cases the serum chloride may be considered slightly elevated, being 412 and 421 mg. per 100 cc. serum. The administration of pituitrin did not alter the results appreciably because the serum chloride concentrations were only a few milligrams above or below those levels when no pituitrin was taken. The diuretic effect of the diabetes insipidus and the antidiuretic of pituitrin did not affect the chlorides in these cases. The chloride determinations were repeated on several occasions in most of the cases, but since the results were much the same, only single determinations are reported in the tables. The serum chloride determined daily or on alternate days will be discussed with the urinary chloride.

TABLE 1—SERUM CHLORIDE IN 22 PATIENTS WITH DIABETES INSIPIDUS WITH AND WITHOUT PITUITRIN ADMINISTRATION

Case No	No pituitrin Serum chloride, Mg per 100 cc	Pituitrin Serum chloride, Mg per 100 cc	Case No	No pituitrin Serum chloride Mg per 100 cc
1	388	394	12	325
2	349	335	13	361
3	347	360	14	421
4	343	360	15	349
5	349	338	16	374
6	364	364	17	347
7	412	370	18	357
8	340	358	19	344
9	364	370	20	358
10	329	355	21	375
11	392	395	22	368

TABLE 2—SERUM CHLORIDE IN 7 PATIENTS WITH DIABETES INSIPIDUS WHO HAD NO PITUITRIN FOR A LONG TIME

Case No	Serum chloride, mg per 100 cc	Daily fluid intake liters	Period without pituitrin
4	343	10-14	2 months
5	340	8-11	Several years
17	347	10	Several years
18	357	7-10	Several years
19	344	7-9	1 year
20	358	4-5	1 year
21	375	8-10	6 months

Total Chloride in Urine. In the first case, the total excretion of chloride† in the urine was determined daily for 28 days on one ad-

* The chlorides in terms of milliequivalents per liter may be obtained by dividing the mg Cl_2 by 3.55, and the gm NaCl per liter by 0.0585.

† See Footnote on previous page

mission to the hospital and the results are shown in Chart 1. This case took exactly 10 gm. of sodium chloride daily which included the amount in the food and the added salt. The observations were made for the first 13 days with pituitrin therapy and the average sodium chloride excretion was 9.7 gm. daily, the daily range being 6.7 to 12 gm. During the next 9 days no pituitrin was given and the daily average sodium chloride excretion was 9.1 gm. with a range of from 6.7 to 11.2 gm. During the last 6 days pituitrin was

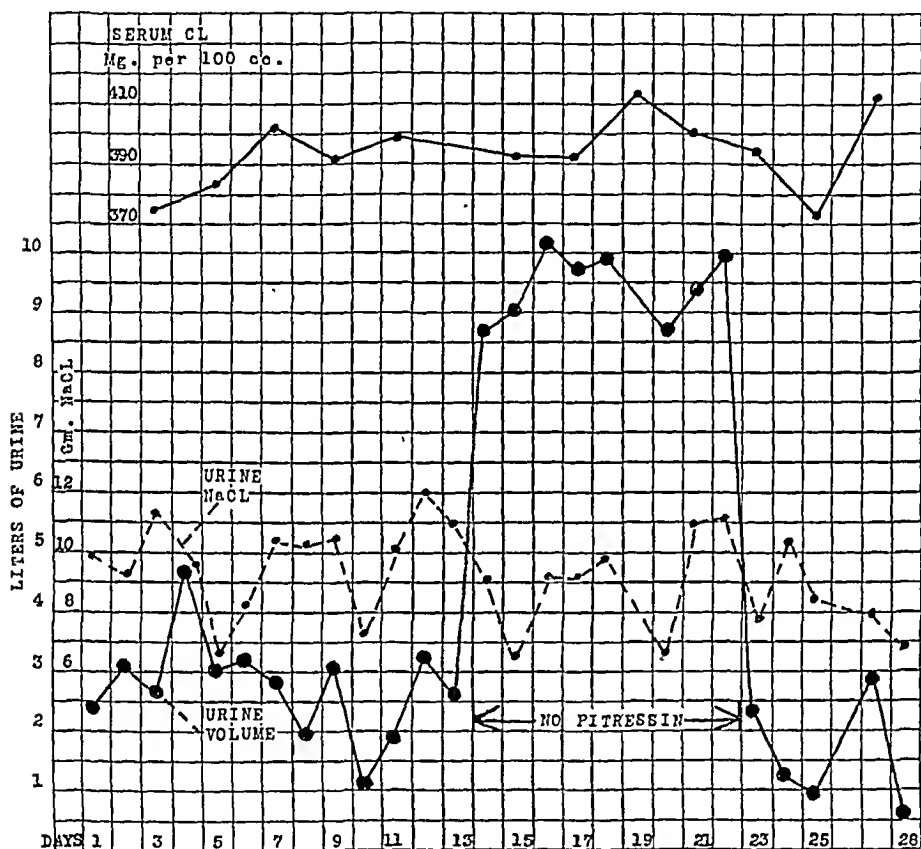


CHART 1.—Daily NaCl excretion and urine output and serum chloride in a patient with diabetes insipidus with and without pituitrin therapy. Diet was constant and contained exactly 10 gm. salt daily. Pitressin 1 cc. was injected every 6 hours. Case 1.

injected again and the average sodium chloride excretion was 8.3 gm. daily, with a range of from 6.8 to 10.4 gm. The serum chloride level showed some slight daily variations whether or not pituitrin was given.

This patient was readmitted to the hospital a month later to observe the effect of restricting the fluid intake on the blood and urine chloride. His sodium chloride intake was exactly 10 gm. daily. The chlorides were determined for 8 days. For the first 4 days pituitrin was administered and the patient took as much fluids as

desired. On the fifth day, pituitrin was omitted and the fluid intake was limited to 3200 cc. and the urine volume was 6050 cc. As the result, he lost approximately 3 kilos in weight and developed such a terrific thirst that he was unable to restrict the fluid intake any longer. The temperature was unaffected. Subsequently, he was given for the next 3 days fluids as desired without pituitrin. The results of this experiment are illustrated in Chart 2. As can be seen here, the serum chloride concentration and the excretion of salt in the urine showed no significant variation during the 8 days of ob-

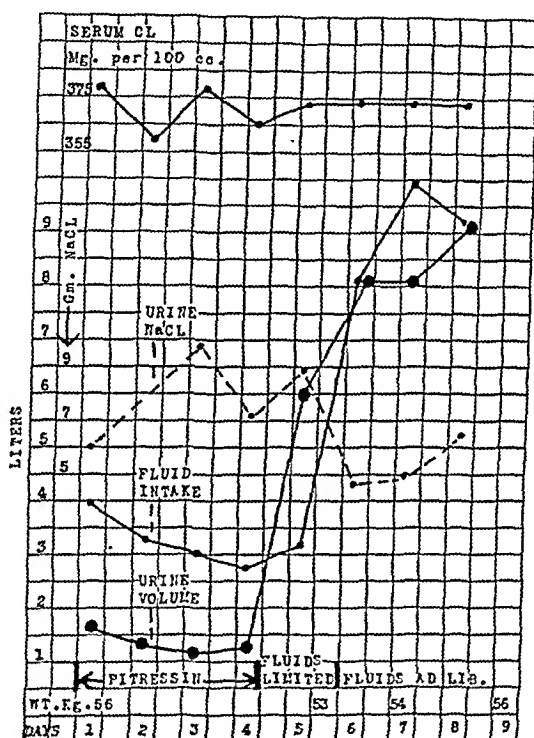


CHART 2.—Effect of restricting the fluid intake without pitressin for 1 day on the NaCl excretion and on the serum chloride in Case 2 with diabetes insipidus. Diet contained exactly 10 gm. salt daily. Pitressin 1 cc. was injected every 8 hours.

servation, regardless of the volume of urine. This was especially true on the day when the fluid intake was restricted which resulted in a considerable loss of weight.

In the second case, the total excretion of chloride in the urine was determined for 18 days when the diet contained approximately 10 gm. of salt daily. The patient had omitted pituitrin and the urine volume was high for a week before admission to the hospital when the studies were commenced. Here the observations were made during the first 5 days without pituitrin therapy, during the

next 10 days with pituitrin injection and finally during the last 3 days again without pituitrin. The daily urine volume was about 13 liters without pituitrin and about 2 liters with pituitrin therapy. In this case, too, there was considerable variation in the daily excretion of salt during the various periods of observations. As the results are so much like those observed in the first case they are not presented in detail here.

A third case of severe diabetes insipidus, observed in the hospital some years ago, was of unusual interest. His daily volume of urine usually ranged from 32,000 to 37,000 cc., although on 1 day the output rose to almost 40,000 cc. His total urinary chloride expressed as sodium chloride was found to be 12.1 gm. during one 24-hour period when the urine was 25,760 cc. This shows that salt is not swept out by the large flow of urine.

Comment. The results of this investigation were interesting because they were consistent and because no changes from the normal were found in the serum chloride concentration in this large group of patients even though large volumes of urine were voided over a long period of time which in some cases was several years. The chloride in the spinal fluid determined in 10 of these patients has already been reported¹ as normal. The daily chloride excretion in the urine, too, was normal, in spite of the fact that the urine volume in 1 case was as high as 25,760 cc. and that in another case the fluid intake was restricted to 3200 cc. for 1 day, where his usual intake is about 10 liters daily without treatment. Pituitrin administration did not appear to produce any significant chloride changes in the blood or urine of these patients. If anything, this drug decreased the salt excretion. These results are in contrast to those in which there were found in diabetes insipidus abnormal changes in the blood chloride concentration and a diminished salt excretion which was stimulated by pituitrin administration. Even in normal persons, Manchester⁸ and Smith and MacKay¹⁶ noted that posterior pituitary extracts produced a large increase in the sodium and chloride excretion in the urine.

A number of investigators have shown that various diuretics increased markedly the chloride excretion in the urine. Among them are Fulton and associates⁶ who found, in addition, in normal dogs that pituitrin inhibited the increased urine volume after novasural but did not prevent the increased chloride excretion. That certain diuretics increase the salt excretion in diabetes insipidus also has been shown. Meyer¹⁰ found in this disease that theocin did not affect the total amount of fluid excreted, but it increased the concentration of sodium chloride in the urine so that during the 24 hours after its administration, the excretion of salt was increased. When theocin was omitted, the chloride output diminished until the normal balance was regained. Fitz⁵ gave theocin and theobromin sodium salicylate which alone had no diuretic action in his case, nor

did they increase the total output of sodium chloride. However, when theocin and additional salt were given together, a larger output of chloride was obtained than when no theocin was included. Lindeboom,⁷ however, obtained in diabetes insipidus a diuretic effect with salyrgan and an unusually high concentration of salt in the urine for this disease, although the blood chloride concentration showed no significant changes. From my experiments, it appears that the diuretic effect of the diabetes insipidus and the antidiuretic effect of pituitrin do not alter the total serum and urine chlorides in these patients.

These cases show that patients with diabetes insipidus maintain a normal chloride balance when they take an ordinary amount of salt in their diet, notwithstanding the exchange of huge volumes of fluid or the administration of pituitrin. The diuretic effect of diabetes insipidus and the antidiuretic effect of pituitrin did not alter the chloride balance in this disease.

Summary. This paper presents a study of the serum chloride concentrations in 22 patients with diabetes insipidus and the total excretion of chloride in the urine of 2 of them.

The serum chloride concentration was found to be normal in these cases, even though some patients had not taken pituitrin for several years. Pituitrin administration did not affect significantly the serum chloride concentration.

The total excretion of chloride in the urine showed some variation from day to day but the results came within the normal range, even though huge volumes of urine were excreted. Pituitrin therapy did not alter the results appreciably. A considerable restriction of the fluid intake in 1 patient for 1 day did not change the serum chloride concentration or the salt excretion in the urine.

Patients with diabetes insipidus taking a normal amount of salt maintain a normal serum and urine chloride balance in spite of the exchange of large volumes of fluid. The diuresis of diabetes insipidus does not affect the serum and urine chlorides like the diuretics in normal people and also the antidiuretic action of pituitrin does not have an opposite action on the chloride balance.

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ADSORPTION OF SURFACE-ACTIVE SUBSTANCES OF URINES, WITH SPECIAL REFERENCE TO MALIGNANT NEOPLASIA.

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NUMEROUS investigations have dealt with the surface tension of the urine and with physiologic and pathologic changes in the excretion of surface active substances. No definite conclusion could be reached concerning the chemical nature of the substances responsible for the lowering of the urinary surface tension. It can, however, be assumed by reviewing the principal urinary constituents that these surface active substances are represented mainly in the following three categories: 1, bile acids and their salts; 2, fatty acids, their salts and esters; 3, products of protein decomposition, such as peptones, albumoses and oxy-proteic acids. While in one specific condition—icterus—it is known that the low surface tension of the urine is caused by increased excretion of bile acids and their salts,⁴ such a chemical identification of the surface active substances has not been possible in various other conditions where lowered surface tension of the urine was encountered. But it seems highly probable that the surface tension of the urine is the result of the excretion of different surface active substances which physiologically and pathologically are subject to changes concerning their quantity and their combination as well.^{2,3,17}

In this paper the adsorbability of the urinary surface active substances has been analyzed. The investigations were carried out with the idea that the qualitatively and quantitatively varying combination of surface active substances should find a more instructive expression in their adsorptive behavior than in the surface tension alone. From this viewpoint a large number of urine specimens was investigated, both derived from normal persons and from persons suffering from various diseases. Among the pathologic cases special interest was turned to malignant tumors, as in this condition, not only an increased amount of surface active substances was found in the neoplasms themselves and in the blood serum of the patients, but also several reports indicated changes in the urinary surface tension.

The basic principle of our study was to determine how much of the surface-active substances of a certain urine specimen could be

adsorbed by a constant quantity of an adsorbent. The adsorbability of the surface-active substances in various urines was tested by successive addition of urine to the adsorbent and by determination of the remaining surface tension—indicating the amount of surface-active substances *not* adsorbed by the employed adsorbent. In tentative experiments it was learned that the treatment of the adsorbent with 5-times 10 cc. of urine permitted a sufficient evaluation of the adsorbability of the urinary surface-active substances.

Procedure. The stalagmometric method was used for the determination of the surface tension of the urine samples and Norit A in the amount of 100 mg. was employed as adsorbent. The first morning specimens of urines were always used, not less than 3 hours and not later than 6 hours after their collection. In all urine samples tests were made for specific gravity, reaction, and presence of albumin. Specimens exhibiting a pH higher than 8—containing an excess of ammonia—and specimens containing albumin were discarded; likewise urines with a specific gravity lower than 1.010. All urines were filtered and those with a specific gravity higher than 1.010 diluted with distilled water to a specific gravity of 1.010. At least 50 cc. of the urine of 1.010 specific gravity were required for one experiment. To 10 parts of the (diluted) urine 1 part of a buffer was added which consisted of equal parts of M/15 monobasic and M/15 dibasic sodium phosphate. In the urine specimen thus prepared stalagmometry was performed, establishing the surface tension of the original sample (γ_0 or γ_o). Then 10 cc. of the urine were added to 100 mg. of Norit A in a centrifuging tube, the mixture was vigorously shaken for 1 minute, centrifuged for 10 minutes at 2,000 turns per minute, and the supernatant liquid passed through a small filter for removal of coal particles floating on the surface. Stalagmometry of this filtrate was done, giving the remaining surface tension (γ_1) of the first 10 cc. of urine, after their adsorption to 100 mg. of Norit A. The same 100 mg. of the adsorbent were now loaded for the second time with 10 cc. of the urine. The mixture was again shaken, centrifuged, run through the same filter and subjected to stalagmometry, furnishing γ_2 . This procedure was repeated 5 times in the same way. The stalagmometry of the fifth sample of 10 cc. of urine, after its adsorption to the original 100 mg. of Norit A, yielded a value of surface tension (γ_5) which indicated how much of the surface-active substances of this sample could not be adsorbed by the adsorbent after it was successively loaded with 50 cc. of the urine. It is obvious that the adsorbability of the surface-active substances contained in the respective urine sample is decisive for the outcome of the experiment. In the case of a high adsorbability the fifth sample would show only a small amount of surface activity, while a strongly surface-active one would indicate a poor adsorbability. By means of a calculation, given below, this relation was expressed by a ratio depending on the original surface tension of the urine (γ_0) and the surface tension of the 5th sample (γ_5). This ratio exhibited certain characteristic variations as may be seen from the tables.

Technical Details. The first morning urine specimens were used because of the desire to avoid dilution of the urine by ingestion of water and/or nutritional influences of food. Furthermore, several authors^{1,11} found daily fluctuations in the surface tension of urine portions voided by the same person during 24 hours; the highest surface activity, lowest surface tension, respectively, was found in the first morning urine, even independent of the intake of food or drink.¹¹ Therefore the use of morning specimens should warrant more uniform and comparable conditions than 24-hour specimens. Besides a 24-hour specimen requires the cooperation of the patient, which is not always reliable, and the addition of a preservative.

Stalagmometry was performed not less than 3 hours after collection of the sample because changes occur during this time in the surface tension of the urine until an equilibrium is reached (time factor⁶). The dilution of the urine to the same specific gravity of 1.010 was done for purposes of uniformity. A similar method was used by Schemensky.¹³ Objections to this dilution were made by Perryman and Selous¹¹ and by Hahn,⁶ who could not find any direct relationship between specific gravity and surface tension. But these objections are not justified when the stalagmometric method, partly depending on the specific gravity, is employed.

By the addition of the buffer the pH of which was 5.8, the urine pH was brought to an average of 6.5 to 6.8, thus insuring the stability of the reaction. This is highly important because strongly acid and strongly alkaline reaction was found to increase the urinary surface activity,^{4,13} and because of the influence of reaction on adsorption. A strongly alkaline reaction—exceeding pH of 8—usually caused by ammoniacal decomposition of the urine—necessitated discarding the sample. In these cases we noted that a high adsorbability of the surface-active substances always prevailed and this was confirmed also in experiments where investigation was first made in the original urine of a pH of 6.8, and then repeated, after alkalinization of the sample with ammonium hydroxide. Likewise albumin-containing specimens were discarded, as the presence of albumin was found to result in a poor adsorbability of the surface-active substances (*cf.* model experiments).

Concerning the choice of charcoal (Norit A) as adsorbent, it must be mentioned that several other substances tested—kaolin, aluminum hydroxide, aluminum silicate, lead acetate and phosphate—did not exhibit any adsorbing capacity for the urinary surface-active substances. Norit A was used because of its defined colloido-chemical structure and high adsorptive quality as compared with other charcoal preparations. The amount of 100 mg. of Norit A was used, since experiments showed this quantity could adsorb practically all the surface-active substances contained in 10 cc. of various urine samples.

The stalagmometric method was employed in this study with full knowledge of the numerous objections raised against its accuracy, as far as the determination of the actual physical value of the surface tension is concerned, and in awareness of the sources of error inherent in this method when used in biological fluids, especially in fluids of a high protein content and viscosity, such as serum.⁷ However, the method was considered efficient enough for this study as, on one side, only comparative values of the surface tension were desired and, on the other hand, the above mentioned precautions were taken to warrant the uniformity of the investigated specimens. It might be mentioned here also that in a recent study on the surface tension of the urine in which, simultaneously, the method of capillary rise, stalagmometry and the method of maximum bubble pressure were used, all these methods were found to agree satisfactorily and stalagmometry to give "the most trustworthy data."⁵

The instrument used was the stalagmometer of Traube (Eimer & Amend, No. 28656), holding approximately 4 cc. The instruments were standardized with distilled water. The daily variations of the room temperature were found to be without noticeable influence. The liquid was brought into the instrument by means of a rubber bulb attached to the top of the stalagmometer. The velocity of the falling drops was constant in the determinations performed with liquids of the same specific gravity and of only slightly varying viscosity. The stalagmometer was cleaned prior to determinations, rinsed first with the specimen and frequently thoroughly cleaned with chromic acid. The foam and liquid adhering to the bottom opening were removed with clean filter paper before the determination, thus excluding an important source of error.⁹ The drops were counted in the

usual way, the fractions of a drop found by means of the graduations below and above the zero points. Every determination was repeated at least twice and agreement within ± 0.1 drop required. The calculation of the surface tension was made according to the equation: $\gamma_1/\gamma_2 = D_1/D_2 \times N_2/N_1$ in which γ_1 represents the unknown surface tension, γ_2 the approximate value of the surface tension of water, D_1 the density of the unknown, D_2 the density of water, N_1 the number of drops with the unknown, N_2 the number of drops with water.

The evaluation of the experiments was made in the following way: the calculated surface tension of the original (diluted and buffered) specimen was marked γ_0 , the surface tension found in the 5th sample of 10 cc. of urine, after its adsorption to the Norit A, as γ_s . The latter value indicated how much of the surface-active substances has not been adsorbed by the 100 mg. Norit A at the end of the experiment. The mathematical relation was expressed by the following ratio (R) between the originally present and the not adsorbable surface-active substances:

$$R = (73.0 \text{ (surface tension of water) minus } \gamma_s) / (73.0 \text{ minus } \gamma_0) \cdot 100.$$

$$\text{Example: } \gamma_0 = 61.9, \gamma_s = 69.6. \quad R = \frac{73.0 - 69.6}{73.0 - 61.9} \cdot 100 = 30.6.$$

Roughly, the ratio of this example could be interpreted as indicating that the 5th treatment of 100 mg. Norit A with 10 cc. of the investigated urine resulted in the failure to adsorb approximately 30% of the originally present surface active substances of the urine specimen used.

TABLE 1.—NORMAL CASES AND VARIOUS DISEASES EXCEPTING MALIGNANCY, ACUTE INFECTION AND TUBERCULOSIS.

Case No	Diagnosis	Gamma ₀ dyn/cm	Gamma _s dyn/cm	R *	Case No	Diagnosis	Gamma ₀ dyn/cm	Gamma _s dyn/cm	R *
1	Contusion of face	59.8	68.4	34.8	25	Fract fibula	67.7	70.5	47.2
2	Fract femur	61.3	69.2	32.5	26	Gastritis	67.7	71.7	24.5
3	Fract femur	61.9	69.6	30.6	27	Fract pelvis	67.7	71.6	26.4
4	Coronary sclerosis	61.9	68.1	44.1	28	Laceration of leg	67.7	70.8	41.5
5	Hemorrhoidectomy	61.9	63.2	70.3	29	Fract femur	67.7	72.0	15.9
6	Contusion of skull	61.9	65.5	67.6	30	Normal	67.9	70.9	41.1
7	Fract of humerus	62.5	68.8	40.0	31	P appendectomy	68.1	71.6	28.6
8	Fract lumbar vert	62.9	69.2	37.6	32	Normal	68.3	71.3	36.2
9	Fissure ani	63.5	67.3	60.0	33	Fract tibia	68.4	72.0	21.7
10	Hemorrhoids	63.9	68.1	53.8	34	Icterus	68.6	72.1	20.5
11	Femoral hernia	64.1	69.0	44.9	35	Hernia	68.8	72.0	23.8
12	Fract tibia	64.2	68.4	52.3	36	Arthritis	68.8	72.9	2.4
13	Prolapsus of rectum	64.8	70.8	26.8	37	Frost bites	68.8	72.9	2.4
14	P. cholecystectomy	65.5	70.8	29.3	38	Normal	68.8	72.4	14.3
15	Liver cirrhosis	65.5	69.7	41.0	39	Normal	69.0	70.9	52.5
16	Fract femur	65.9	71.6	19.7	40	Hypertension	69.2	72.0	26.9
17	Hemorrhoids	66.2	70.0	44.1	41	Fract femur	69.6	72.0	29.4
18	Burns	66.2	70.4	38.2	42	Fract femur	69.6	72.0	29.4
19	Fract femur	67.0	70.8	36.7	43	Varix of groin	69.6	72.4	17.6
20	Fract ribs	67.0	70.8	36.7	44	Fract fibula	69.6	72.0	29.4
21	Fract. tibia	67.0	71.6	23.4	45	Cardiac condition	70.0	72.0	33.3
22	Contusion of back	67.0	70.8	36.7	46	Peptic ulcer	70.1	72.5	17.2
23	Arthritis	67.3	70.8	38.6	47	Peptic ulcer	70.8	72.9	4.6
24	Fract of hip	67.3	72.0	17.5					

* In this and following tables, R = ratio between the originally present and the not adsorbable surface-active substances.

In Tables 1 to 4 118 cases are summarized, the urines of which have been analyzed according to the described procedure. Table 1 contains 47 cases, 21 of which concern urines either of normal persons or of patients with bone fractures or contusions, who also may be regarded as normal as to their metabolic functions. The remaining 26 patients were suffering from various ailments. The surface tension of the (diluted, buffered) urines ranged from 59.8 to 70.8 dyn cm, the average value being 66.6. In testing the adsorb-

bility of the surface-active substances of these urines, R-values varied between 2.4 to 70.3 (average, 32.9). Of these 46 cases 41 showed R-values lower than 50, and only 6 (approximately 13%) exhibited higher values.

TABLE 2.—CANCER.

Case No.	Carcinoma of	Gamma ₀ dyn./cm.	Gamma _s dyn./cm.	R.	Case No.	Carcinoma of	Gamma ₀ dyn./cm.	Gamma _s dyn./cm.	R.
1	Cervix	53.2	57.9	76.8	28	Larynx	65.5	70.0	68.4
2	Lip	56.8	59.6	82.7	29	Breast	65.5	68.4	64.0
3	Tongue	58.3	60.2	87.1	30	Cervix	65.9	67.7	74.6
4	Cervix	58.8	65.5	52.8	31	Breast	65.9	69.2	53.5
5	Cervix	59.8	62.5	79.5	32	Gall bladder	66.2	68.8	61.8
6	Lymphogranuloma . .	60.1	62.2	83.7	33	Larynx	66.5	69.0	61.5
7	Larynx	61.0	65.2	65.0	34	Cervix	66.5	68.6	67.7
8	Cervix	61.2	63.5	83.1	35	Rodent ulcer of face .	66.5	71.2	27.7
9	Lip	61.6	65.9	65.7	36	Cervix	66.5	69.0	61.5
10	Esophagus	62.5	65.9	65.7	37	Breast	66.8	69.3	59.7
11	Esophagus	62.5	64.5	81.0	38	Face	67.0	70.0	50.0
12	Lung	62.9	66.2	67.3	39	Rectum	67.0	70.4	43.3
13	Cervix	63.2	66.5	66.3	40	Rectum	67.3	69.6	59.7
14	Cervix	63.2	66.5	66.3	41	Larynx	67.7	70.4	49.1
15	Esophagus	63.5	66.2	71.6	42	Esophagus	67.7	69.7	62.3
16	Esophagus	63.5	65.9	74.7	43	Floor of mouth	67.7	70.8	41.5
17	Schmincke tumor . .	63.9	66.5	71.4	44	Breast	68.1	70.8	44.9
18	Tongue	63.9	67.3	62.6	45	Floor of mouth	68.1	72.0	20.4
19	Cervix	63.9	67.7	58.2	46	Cervix	68.4	72.0	2.2
20	Jaw	63.9	67.3	62.6	47	Breast	68.6	70.5	56.8
21	Tongue	64.2	67.7	60.2	48	Larynx	68.8	70.8	52.4
22	Cervix	64.5	67.3	67.1	49	Chondrosarcoma of leg	68.8	69.2	90.4
23	Tongue	64.5	68.1	57.6	50	Rectum	69.2	70.4	68.4
24	Cervix	64.8	68.4	56.1	51	Tongue	69.2	72.4	15.8
25	Stomach	64.8	68.1	59.8	52	Cervix	70.4	72.0	38.6
26	Rectum	65.1	68.6	55.1	53	Breast	70.4	72.4	23.1
27	Sarcoma of maxilla .	65.2	67.7	68.0					

TABLE 3.—INFECTIONS.

Case No.	Diagnosis.	Gamma ₀ dyn./cm.	Gamma _s dyn./cm.	R.	Case No.	Diagnosis.	Gamma ₀ dyn./cm.	Gamma _s dyn./cm.	R.
1	Erysipelas	59.0	61.3	83.6	5	Pneumonia	65.5	66.8	82.7
2	Pneumonia	64.2	67.7	60.2	6	Infect. of thumb . . .	66.5	69.2	58.5
3	Actinomyces	65.2	68.8	53.8	7	Infect. of hand	67.7	71.2	34.0
4	Cellulitis of leg . .	65.2	68.8	53.8	8	Empyema	70.8	72.9	4.6

TABLE 4. TUBERCULOSIS.

Case No.	Diagnosis.	Gamma ₀ dyn./cm.	Gamma _s dyn./cm.	R.	Case No.	Diagnosis.	Gamma ₀ dyn./cm.	Gamma _s dyn./cm.	R.
1	Cavernous TB	53.7	63.5	49.2	6	Acute pulmon. TB . . .	66.1	70.1	44.6
2	Acute pulmon. TB . .	62.6	65.8	69.2	7	Cavity in RUL	66.5	70.1	44.6
3	Bilateral cavities . .	64.5	68.6	51.8	8	Acute TB pneumonia . .	66.5	69.3	56.9
4	Acute pulmon. TB . .	64.8	69.0	48.8	9	Cavities in RUL	66.5	70.1	44.6
5	Fibroid cavernous TB	65.1	68.6	55.7	10	TB pneumonia	66.8	69.7	53.2

TABLE 5.—MODEL EXPERIMENTS.

Solution, %.		Gamma ₀ dyn./cm.	Gamma _s dyn./cm.	R.
0.007	Sodium oleate	49.9	73.0	0.0
0.035	Sodium oleate	27.0	68.4	10.0
0.015	Sodium cholate	64.5	71.3	20.0
0.02	Sodium cholate	60.7	70.0	24.4
0.04	Sodium cholate	57.6	64.5	55.2
0.1	Saponin	66.2	68.4	67.6
0.15	Saponin	65.2	67.7	67.9
1.0	Peptone	59.6	60.5	93.3
0.25	Egg-albumin	69.2	70.4	68.4

Quite different are the results summarized in Table 2, dealing with 53 cases of malignant tumors. In these urines the surface tension ranges from

53.2 to 70.4 (average, 64.8 dyn/cm). R ranges from 2.2 to 90.4 (average, 59.8). In 43 out of these 53 cases the R -values were found higher than 50, while in 10 (approximately 19%) lower values were observed. Furthermore, 8 cases of acute infections and 10 cases of pulmonary tuberculosis were tested, appearing in Tables 3 and 4, respectively. Although the number of these latter cases is very small, the results are uniform enough: the values for R in 6 out of the 8 infectious cases are above 50 (average, 53.9); while in the tuberculosis urines an average of 51.1 was found for R .

In analyzing these results, the following inferences are made:

1. While the surface tension of the urines derived from patients with malignant neoplasms generally appears to be lower, as expressed in the average value of 64.8 dyn/cm as compared with the respective value of 66.6 dyn/cm obtained in the cases free from malignancy, the surface tension value found in a single case does not present a characteristic means of differentiation between "malignant" and "non-malignant" urines. Taking the value of 66.6 dyn/cm as the "normal" average in our experiments, we find in the "non-malignant" cases (Table 1) 18 out of 47 cases (approximately 39%) exhibiting lower values, whereas in malignant cases (Table 2) 36 out of 53 urines (approximately 68%) belong to this category. To put it simply: among "non-malignant" urines we find 2 out of 5 specimens and in "malignant" cases 2 out of 3 samples which exhibit surface tension values below the "normal" average.

2. Far more characteristic are the findings which were obtained by studying the adsorbability of the urinary surface-active substances, as indicated by the factor R . Assuming 50 as the critical value for R , which, as explained above, indicates that at the end of the experiment 50% of the surface-active substances failed to be adsorbed, we find in the "non-malignant" urines in approximately 87% R -values below 50, and in the "malignant" cases approximately 79% above 50, thus indicating clearly the poorer adsorbability of the surface-active substances contained in the urines of patients afflicted with malignant neoplasms.

3. This difference in the adsorbability of the surface-active substances does not depend on the original surface tension, as may be easily seen from the tables. Comparison of Tables 1 and 2 reveals several identical or similar values of the original surface tension (γ_0) which are connected with widely varying adsorbability as expressed by R . High adsorbability was observed in urines with very low surface tension and *vice versa*. There is, however, one exception which concerns some "malignant" urines (Table 2, 50 to 53) containing small amounts of surface-active substances, indicated by their high surface tension, and at the same time showing a better adsorbability—within the range of normal values.

4. In the analyzed malignant cases no connection could be established between the extent and severity of the disease on the one side, and between the urinary surface tension and/or the adsorbability on the other side. That is, the results mentioned are not expressions

of the generally impaired condition of the patients, nor can they be attributed to special localizations of the tumors. It seems, however, that the impaired adsorptive quality of the urinary surface-active substances may be more marked in cases where internal tumors existed, as 6 out of the 10 "malignant" urines with normal R-values concerned external tumors, such as face, tongue, and not metastasized breast neoplasms.

5: The few investigated cases of acute infections (Table 3) and of acute pulmonary tuberculosis (Table 4) yielded results very similar to the findings in the malignant neoplasms as regards adsorbability of the surface-active substances. An extremely low adsorbability was observed in 2 cases of pneumonia, while the adsorption in urines of tuberculosis was characterized by values ranging mostly around 50.

Thus a characteristic quality of the surface-active substances concerning their adsorbability was found in the majority of cases of malignant neoplasia and also of acute infections, as compared with the respective behavior of the surface-active substances in urines of normal persons or persons with other diseases than cancer or acute infections. This difference certainly depends on the chemical character of the surface-active substances contained in the different urine categories. However, the most desirable proof for this assumption, the direct chemical analysis, encountered essential difficulties, primarily because all attempts failed to recover the adsorbed surface-active substance from the adsorbent by elution (*cf.* Bechhold and Reiner³). Therefore, another indirect way was chosen, that is, studying in model experiments the adsorptive behavior of several biologically important surface-active substances. As representatives of 4 groups of this kind sodium oleate (fatty acids), sodium cholate (bile acids), saponin, peptone and albumin (protein and protein decomposition products) were analyzed. As outlined above, the surface active-substances of the urine are most probably combined from these groups with the exception of saponin-like substances which may appear in the body and urine as a result of medication only. The results of these experiments, which were performed in the same way as the experiments with urines, are contained in Table 5.

In comparing these results we find the best adsorbability present in sodium oleate solutions as expressed in a R of 10.0, combined with an original surface tension as low as 27.0 dyn/cm. The reverse property—very poor adsorbability—was observed in peptone solutions—R-93.3 (γ_0 -59.6 dyn/cm) and in albumin solutions—R-68.4 (γ_0 -69.2). Between these extremes, cholate maintains a middle position with an adsorption: R-21.0, 24.4, 55.2 for the respective surface tensions of 64.5, 60.7 and 57.6 dyn/cm. A poor adsorption was found for saponin also (R 67.6, 67.9), but, as explained above, saponin does not have special significance in relation to the surface-active substances of the urine.

On the basis of these model experiments, the conclusion appears to be justified that the surface-active substances present in "normal" urines consist, according to their adsorbability, of varying combinations of fatty acids, bile acids, and their salts, respectively. In malignancy, however, and in other urine specimens exhibiting a decreased adsorbability, protein decomposition products, such as peptones, albumoses and oxyproteic acids, must be considered responsible for the lowered surface tension and the diminished adsorbability of the urinary surface-active substances.

A short review of the literature reveals that these results agree very well with previous findings on urinary surface tension, and they also fit satisfactorily into our knowledge of metabolism in neoplasia. With the exception of the direct relation between lowered surface tension and increased bile acid content of the urine in icterus, no definite connection between any pathologic condition and the urinary surface tension could be established.¹¹ Also, kidney diseases—both of surgical and medical—were shown to be without influence on the urinary surface tension.¹⁰ With regard to the chemical nature of the urinary surface-active substances, Traube and Blumenthal¹⁵ assumed that peptones and other protein decomposition products are to be found among them. Bechhold and Reiner³ made a similar statement on the basis of their investigations.

Several papers were concerned directly with the urinary surface tension of neoplastic patients. Schemensky¹³ mainly studied the effect of acidification of urine on its surface tension. This procedure regularly caused a rise of the surface activity but was more effective in urines of patients with malignant neoplasms. The author found this quality so characteristic that he proposed its diagnostic utilization. While the lowering of the surface tension after acidification of urine was confirmed¹ and in the course of this study similar observations were made, Isaac-Krieger and Friedländer⁹ found no diagnostic usefulness of this method. Only 11 of 24 cancer urines showed an "acid effect" exceeding the normal range, whereas "positive" results were obtained in a high percentage of control cases also. From a different angle Adlersberg and Sugar¹ approached this subject by studying the daily fluctuation of the surface tension in urine portions passed within 24 hours. The authors observed in malignancy, as well as in a number of other diseases, such as consumptive tuberculosis, liver diseases and albuminuria, a lesser degree of daily changes in the surface tension than in "normal" cases. This phenomenon was called "iso-stalecturia" and was considered evidence of the presence of protein decomposition products.

On the other hand, it is well known from numerous investigations that the pathologic protein metabolism in malignant neoplasia results in changes of the N-containing substances in the urine. We refer mainly to studies on the "colloidal N" and the oxyproteic acids (Salomon and Saxl¹²). The increased urinary excretion of

these substances in malignancy was studied by several authors (cf.^{16a}).

This study attempted to clarify the problem insofar as the relation between urinary surface-active substances and excretion of protein decomposition products is concerned. No connection between disease and the value of the urinary surface tension could be established. But in malignancy and in acute infections a characteristic adsorptive quality of the surface active substances was observed. While it is obvious that this quality does not lend itself to diagnostic purposes, it offers some insight into the metabolic processes of these diseases.

In this connection the following possibility may be mentioned purely hypothetically. Protein decomposition products do arise in the body during normal and many other pathologic conditions also. Because of their colloidal character, however, they are stored by the reticulo-endothelial system, as far as they are not destroyed. Both in malignancy and in acute infections, in which conditions we noted the presence of increased amounts of protein decomposition products in the urine, the reticulo-endothelial system was found to be functionally impaired.^{14,16b} Therefore a connection between these two phenomena seems to be possible. Adequate animal experiments to clarify this question could not now be performed but will be attempted later if possible.

Summary. Studies on the surface tension and on the adsorption of the surface-active substances were performed in 118 urines. These specimens were derived from normal persons and from patients suffering from various diseases. In the majority of the urines of patients afflicted with malignant neoplasms, acute infections, or tuberculosis, a characteristic quality of the urinary surface active substances was observed with regard to their adsorbability. These results were connected with the chemical nature of the surface-active substances, and their significance for the understanding of metabolic processes was discussed.

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CARCINOMA OF THE PAPILLA OF VATER: CLINICAL FEATURES IN FORTY CASES.

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CARCINOMA of the papilla of Vater presents an interesting problem. Ampullary carcinomas are small, give rise to symptoms early in the course of the disease and metastasize late. Timely diagnosis of organic disease in these cases should be possible, because obstruction of the vital common bile duct and pancreatic ducts produces easily recognized symptoms. That the cause of the obstruction is carcinoma of the papilla, however, cannot usually be ascertained until operation or necropsy. Surgical treatment offers cure or palliation.

The 40 cases of carcinoma of the papilla of Vater forming the basis of this study are only a part of the cases of this type which have been recognized surgically at the clinic. We have chosen to review only those 40 in which the location and the carcinomatous character of the lesion were confirmed by surgical exploration and biopsy or by necropsy. Some type of operation was performed in 33 of these 40 cases, but specimens for microscopic study were obtained at operation in only 7. Also, in 33 the diagnosis was confirmed by necropsy.

Incidence and Material. Carcinoma in the region of the papilla of Vater is not so rare as one would believe from the relatively few reports in the literature; in fact, it is not uncommon. Cooper and Baggenstoss stated that the lesion can be demonstrated in about 0.2% of all postmortem examinations. Most writers accept 55 years as the average age at which the disease occurs but others reporting series of cases have observed, as we have in this study, that the incidence extends from youth to old age. In this series of 40 cases the youngest patient was 26 years of age, the oldest 67; 27 patients were in the sixth or seventh decades of life. The disease is much more common among men than among women, the ratio varying in different estimates from 2:1 to 6:1. Of the patients concerned in this study 34 were men and 6 were women.

Baggenstoss¹ recently studied, grossly and microscopically, the resected tissue in 28 of the 33 cases herein reported in which necropsy was made. The classic studies of Cohen and Colp,² Crohn,³ and Outerbridge¹⁰ should be mentioned in any review of the subject of carcinoma of ampulla of Vater.

Clinical Features. The anatomic arrangement in the region of the papilla or of the ampulla leads naturally to the development of

obstruction of the common bile duct and pancreatic ducts and to the production of symptoms. It is interesting that in the series under discussion the possibility of carcinoma of the ampulla was suggested in only 1 case, before operation, but in 38 the diagnoses indicated that the clinician knew that obstruction of the common bile duct was present (Table 1).

TABLE 1.—VARIOUS PREOPERATIVE DIAGNOSES AND THEIR INCIDENCE IN 40 CASES OF CARCINOMA OF THE PAPILLA OF VATER.

Diagnosis.	Incidence.
Carcinoma of pancreas	15
Stone in common duct	9
Obstruction of common duct	9
Stricture of common duct	4
Cholecystitis	2
Cirrhosis of the liver	1
Hepatogenous jaundice	1
Intra-abdominal malignant disease	1
Carcinoma of ampulla	1
Empyema of gall bladder	1
Carcinoma of ovary	1
Duodenal ulcer	1
Carcinoma of liver	1
	—
	47*

*. In 7 cases two diagnoses were made.

Since Musser,⁹ in 1889, called attention to the association of symptoms, jaundice has been an accepted feature of carcinoma of the papilla. Through the years the only point of argument has been whether or not the jaundice is intermittent or constant. In this series of 40 cases jaundice was a constant feature, being definitely present in 38 when the patients were admitted to the clinic and developing in the other 2 cases while the patients were under observation. In more than half of the cases jaundice was of a degree sufficient for it to be one of the chief complaints. In 8 cases, jaundice was intermittent, the patients having recovered from one or more attacks in the months or years preceding the final episode. In 32 cases jaundice was constantly present although fluctuating. In a few instances it was said to be non-fluctuating. A mildly fluctuating, slowly progressing jaundice, usually of much less intensity than the progressive icterus of carcinoma of the pancreas, and occurring only once in each case, was the most frequently described type. The greatest period of fluctuating jaundice was 24 months and it is interesting that for long intervals this presenting symptom was unaccompanied by any other disturbance. The longest spell of continuous, non-fluctuating jaundice was 5 months. In cases marked by protracted, fluctuating jaundice, the outstanding symptoms early in the course of the disease were anorexia and gradual loss of weight, whereas pain, nausea and vomiting occurred late. In the smaller group of cases in which the jaundice was non-fluctuating the patients were worse and their course was more rapidly

downhill. Loss of weight and strength was a consistent feature; more than 90% of patients in this group lost weight, 1 patient 60 pounds (27.2 kg.) in 4 months.

Contrary to earlier opinions,^{3,7,8a,b,11} carcinoma of the papilla of Vater is not painless. Twenty-four of the 40 patients had experienced pain of some kind, and pain was one of the chief complaints of 16 of the 24 patients. In 11 of these 24 cases the pain may have been at least partially due to a stone that was present in the common duct, but not necessarily so, for as we shall see later, pain similar to that produced by stone occurred in cases without either cholelithiasis or choledocholithiasis (Case 2). The pain was either colicky or mild and continuous. In general, the milder, continuous type of epigastric pain, together with some tenderness in the right upper abdominal quadrant, was the more frequent finding. In 1 case vague abdominal pain had recurred at intervals in the 48 months prior to the onset of the final episode. In an additional 14 cases abdominal pain of greater or lesser severity preceded the final episode of pain or jaundice.

Chills and fever have been reported to be present in from 12 to 33% of cases of carcinoma of the papilla. These symptoms were present in a larger proportion of cases in this series, being described by 22 of the 40 patients. The finding of stone in the common duct at operation in 10 of these 22 cases indicates that the stones had something to do with the chills and fever. Ninety per cent of our patients experienced nausea at some time, and nausea and vomiting accompanied the more severe attacks of pain and even a good proportion of the milder attacks. Pruritus, naturally, was a troublesome symptom in view of the duration of jaundice and the intensity of damage to the liver in many of these cases.

The descriptions given by the patients of behavior of bowel function presented a number of interesting points in addition to the tendency to acholic stools and dark urine. It is particularly interesting that in 10 of the 38 cases in which the color of the stool was described, tarry stools had been noted by the patients, indicating bleeding from the surface of the tumor; the tendency to bleed will be discussed later. Diarrhea was described as being present in 22 cases. The stools were steatorrheal in a small number of cases.

A number of reports of cases are presented in abstract to illustrate various types of jaundice, with and without pain. These reports illustrate clearly that no typical clinical syndrome may be attached to carcinoma of the papilla.

Painless Intermittent Jaundice. CASE 1.—A man, aged 50, registered at the clinic April 17, 1935. In December, 1933, he had had an attack of painless jaundice associated with severe pruritus, anorexia, loss of weight and extreme fatigue which had persisted for 3 months. The patient had been able to return to work but did not fully recover his strength. In December, 1934, a similar episode of jaundice had begun with diarrhea. No pain was

present, the jaundice fluctuated in severity, the stools were alternately acholic and pigmented.

Physical examination at the clinic revealed the jaundice to be fairly deep and the liver enlarged. A mass that presented the physical characteristics typical of the distended gall bladder of malignant obstruction was palpated in the right upper abdominal quadrant. The concentration of bilirubin was 14 mg. per 100 cc. of serum; results of the Schmidt test for urobilin in the stools were consistently negative. The activity of lipase in the blood serum in terms of twentieth-normal solution of sodium hydroxide ranged around 2 cc. Diagnosis was made of carcinoma of the head of the pancreas. Exploratory operation disclosed the head of the pancreas to be hard and nodular and the gall bladder to be distended, containing two small stones; cholecystogastrostomy was performed. Necropsy revealed carcinoma of the papilla of Vater.

In the foregoing case the jaundice was not only intermittent but in the last attack fluctuating as well. It is possible that the primary attack of jaundice was intrahepatic in origin and unrelated to the terminal attack. It may be assumed however that the onset of jaundice was the first manifestation of the carcinomatous obstruction of the common bile duct, and that the obstruction subsequently disappeared through ulceration of the neoplasm only to reappear after an interval of 9 months. At the time of admission the distended gall bladder and the persistently negative results of the Schmidt test for urobilin in the stools left no doubt that the jaundice was due to obstruction or that the obstruction was a malignant lesion. The palpable gall bladder and the elevation of lipase in the serum pointed to the pancreas or the papilla as the site of the lesion. Further differential diagnosis being impossible, the painless intermittent jaundice was ascribed to the most frequent cause, and clinical diagnosis was made of carcinoma of the head of the pancreas.

Painful Intermittent Jaundice. Case 2.—A woman, aged 48, registered at the clinic Sept. 9, 1933, complaining of abdominal pain which she had had at intervals over a period of 18 months. The first attack had lasted a number of hours, had been associated with chills and fever, and had been followed by jaundice, acholic stools and dark urine that had continued for about 4 days. Seven months later, or 11 months before the patient's admission to the clinic, a seizure of severe colic in the right upper abdominal quadrant, lasting 6 hours, necessitated morphine for relief; this attack likewise was followed by jaundice, chills and fever. The jaundice had persisted 2 months and during this time the patient had repeated attacks of pain, chills and fever. Eight months later, or 3 months before admission a similar attack had begun and had persisted with fluctuating jaundice until registration. On examination it was learned that the patient had lost 28 pounds (12.7 kg.); she was emaciated and deeply jaundiced; the abdomen was distended, the liver enlarged and the palpable gall bladder presented the characteristics of the distended gall bladder of malignant obstruction. The concentration of bilirubin in the serum ranged around 15 mg. per 100 cc. and the van den Bergh reaction was direct. Results of chemical analysis of the stools for bile were consistently negative but small amounts of bile were obtained by the duodenal tube from the duodenal cavity. Exploratory operation revealed ascites, multiple metastatic lesions in the liver and a mass in the region of the head of the pancreas; necropsy disclosed a large carcinoma of the ampulla of Vater.

A more typical story of stone in the common duct could not be written than in the case just reported. The jaundice was painful and was definitely intermittent and obstructive. The degree of obstruction on the patient's admission to the clinic was indicated by the small amount of bile obtained through the duodenal tube and by the negative results of tests for bile in the stools. The palpable mass in the right upper quadrant of the abdomen might have been mistaken for empyema of the gall bladder but its physical characteristics led to the belief that the gall bladder was distended because of malignant obstruction. Stones were not found in either the gall bladder or the common bile duct at operation or at necropsy. There seems little reason for doubting that the carcinoma of the papilla was responsible for the recurring attacks of pain, chills, fever and jaundice.

In many cases of carcinoma of the papilla in which a story of common duct stone is obtained, stones as well as carcinoma are found; when both are present one may wonder, in view of the case just described and of similar cases, whether stone or carcinoma is responsible for the pain.

Painless Constant Jaundice. CASE 3.—A man, aged 53, was admitted to the hospital Oct. 17, 1938. Painless jaundice, mild but fluctuating in intensity, had begun in August of that year and had been accompanied by pruritus, light stools and dark urine. The concentration of bilirubin was 8 mg. per 100 cc. of serum; a normal amount of good bile was obtained by duodenal tube. During hospitalization the patient gained weight, his condition improved, concentration of bilirubin dropped to 2.0 mg. per 100 cc. of serum, and the jaundice decreased. It was assumed that the jaundice was probably intrahepatic in origin and the patient was dismissed Nov. 4.

The jaundice did not entirely clear, it continued to fluctuate in depth, and the patient again began to lose weight. At the time of his second admission to the clinic, Apr. 3, 1939, the jaundice was mild, the concentration of bilirubin was 12.0 mg. per 100 cc. of serum, the activity of lipase in the blood serum in terms of twentieth-normal solution of sodium hydroxide was 3 cc. Abdominal examination gave negative results. Duodenal drainage produced a satisfactory amount of bile which appeared normal but contained some old and some fresh blood. Exploratory operation revealed ascites, marked biliary cirrhosis, a distended gall bladder and an ampullary tumor measuring 2 by 1.5 cm. in diameter. Cholecystogastrostomy was performed as a palliative measure. Death occurred 8 months postoperatively.

The obstruction in the foregoing case was incomplete on each of two examinations of the patient at the clinic; a normal amount of good bile was recovered by duodenal tube and the concentration of bilirubin at the highest was between 8 mg. and 12 mg. per 100 cc. of serum. The jaundice was constant but distinctly fluctuating. The apparent patency of the common bile duct, as indicated by the foregoing findings, as well as the general improvement in the patient's condition, justified the tentative diagnosis of intrahepatic jaundice at the first admission. At the time of the second admission the

picture had changed in certain essentials. The increased activity of lipase in the serum pointed definitely to primary or secondary pancreatic involvement and this, together with the blood in the duodenal contents, suggested an ulcerating and bleeding malignant lesion of the pancreas or the papilla. It is interesting that in spite of the partial patency of the common bile duct the gall bladder at surgical exploration was found to be distended.

Diagnosis. Carcinomas of the papilla have manifested themselves by combinations of symptoms other than those described: by recurrent pain with chills and fever without jaundice until the terminal attack; by constant, fluctuating jaundice with chills and fever but no pain; by progressive non-fluctuating jaundice alone. In 1 case the anorexia and loss of weight overshadowed all other symptoms. It is clear that the clinical picture cannot be relied on for early diagnosis.

Certain physical and laboratory findings serve to establish the obstructive nature of the jaundice and the malignant character of the obstruction. In 25 of the 40 cases distended gall bladders were palpated; in 6 more cases tremendously distended gall bladders were found at operation. Distention of the gall bladder may occur even when the common bile duct is only partially occluded, as in Case 3, and it is undoubtedly the most important finding encountered in cases of carcinoma of the papilla inasmuch as it points definitely to malignant obstruction, as in Cases 1 and 2. Probably in all, or nearly all, cases the gall bladders are enlarged, but not all the gall bladders are felt on examination, since the palpability of the organ depends on the degree of muscular development and relaxation as well as on obesity. Most curious was the disappearance of the distention of the gall bladder in 4 cases, prior to operation; in 1 case after severe upper abdominal pain the gall bladder literally vanished beneath the examiner's fingers. In this case an ulcerating carcinoma of the ampulla was found, and we believe that disappearance of the distention of the gall bladder is to be explained on the basis of recanalization or ulceration of the carcinoma.

Roentgenologic examination has not proved of great value in diagnosis of carcinoma of the region of the papilla. Of the cases here presented the gall bladders were examined roentgenologically in 10, and it is interesting that in 7 the gall bladder functioned normally in spite of existing jaundice. In 3, the roentgenologic finding of non-functioning gall bladders containing stones served only to confuse the diagnosis. Thirty of the 40 patients were subjected to roentgenologic examination of the stomach and duodenum. This procedure likewise proved to be of little value, the results being negative in 20 cases and showing some type of deformity of the duodenum, interpreted as duodenitis, flattening from extrinsic pressure and duodenal ulcer, in the 10 cases.

In 25 of the 40 cases considerable information of value was obtained by examination of duodenal contents removed through the duodenal tube. Bile was absent in 14 cases, indicating the obstructive nature of the jaundice; blood and bile were present in 3 instances, and blood alone in 8, indicating that the lesion was ulcerating and bleeding. It is important to know that evidence of bleeding was discovered by examining the duodenal contents in 44% of the 25 cases.

Data of considerable value likewise were obtained by chemical examinations of the stools and urine; that the stools were acholic and the urine bile-containing is not sufficient comment. More important was the finding of occult blood in 15 cases other than the 10 in which tarry stools had been noted by the patients. Denechau, Tonguy and Varangot⁵ (1931) have called attention to the frequency of occult blood in the stools in carcinoma of the papilla. The tendency for ampullary lesions to bleed is very definite; even fatal hemorrhage has been reported (Halsted,⁶ Cooper³).

Blood counts not infrequently disclose anemia. Determinations of the concentration of bilirubin evidence the depth of jaundice and when carried out frequently, reveal the fluctuations in depth. In this series the concentration of bilirubin ranged from 1.0 mg. to 28.8 mg. and averaged 14.6 mg. per 100 cc. of serum. The van den Bergh reaction was direct in all cases. The determinations of enzymes in the serum have shown increased activity in approximately 66% of cases; such elevated values however do not often aid in distinguishing among various types of pancreatic disease. Determinations of enzymes in the duodenal content were not carried out to any extent in this series. Various tests of hepatic function have been of little assistance in cases of this type.

Differential Diagnosis. Jaundice due to carcinoma of the papilla must be distinguished from jaundice of hepatogenic origin when the duct is patent; that is, when there is bile in the duodenal contents, the gall bladder not palpable and pain is absent. Absence of enzymes from the duodenal contents, and presence of elevated values for amylase and lipase in the serum, and of glycosuria and hyperglycemia, if known to have been absent prior to the onset of the disease, will point to pancreatic involvement and away from a primary intrahepatic disease. Such findings, however, will not denote the nature of the pancreatic disease; gross or occult bleeding is strong evidence of a malignant lesion of the pancreas or of the papilla.

Carcinoma of the papilla must be distinguished from stone in the common bile duct when the jaundice is fluctuating and pain has been, or is, present. If a distended gall bladder characteristic of malignant obstruction is palpated, it may be assumed that malignant disease, with or without stone, is present; but if the gall bladder

is not palpated and the obstruction is incomplete, the malignant character of the lesion may be suspected from the progressive course of the disease and especially if gross or microscopic bleeding is present. Functional tests of the pancreas will denote whether or not the pancreas is involved but will not reveal the character or location of the primary lesion and will not exclude the existence of disease of the biliary tract as well as of pancreatic disease.

Carcinoma of the papilla can be distinguished from carcinoma of the pancreas only with the greatest difficulty. Long continued, fluctuating jaundice together with partial obstruction of the common bile duct and a palpable gall bladder will suggest carcinoma of the papilla but similar clinical pictures are seen in carcinoma of the head of the pancreas. Similarly, blood in the duodenal contents will not serve to distinguish the 2 processes, since bleeding may occur in carcinoma of the head of the pancreas, owing to ulceration into the duodenal wall.

Comment. The diagnosis of carcinoma of the papilla is difficult because the disease presents no typical clinical picture and no typical physical findings. It simulates both benign and malignant obstruction and with the exception of occasional cases in which the findings point to hepatogenic jaundice, the jaundice is obviously obstructive and can be corrected by surgical intervention. Even in the presence of jaundice simulating hepatogenic jaundice, careful observation will disclose developments pointing to the obstructive nature of the process. The hope for successful surgical treatment of carcinoma of the papilla lies in the fact that the picture, even in the early course, is typical of organic disease. Increased awareness on the part of the surgeon of the possibility and of the frequency of carcinomatous involvement of the region of the papilla eventually may evolve satisfactory surgical approach to the treatment of these lesions, as described by Whipple.^{12,13} Preoperative and postoperative care has advanced sufficiently greatly to reduce the operative mortality. Surgical measures such as cholecystogastrostomy offer much from a palliative standpoint, when removal of the carcinoma is not feasible.

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AN ANALYSIS OF THE DIABETIC MORBIDITY AND MORTALITY IN A GENERAL HOSPITAL.

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VARIOUS statistical analyses attempting to evaluate the changes wrought by the introduction of insulin therapy agree that the life expectancy of the diabetic has greatly increased; that coma and sepsis have greatly decreased as causes of diabetic death; and that the percentage of deaths due to arteriosclerotic complications has not been altered appreciably.

These analyses have concerned themselves with the actual causes of mortality. The amenability to insulin therapy of certain complications has removed these from the mortality column and thus may lead to underestimation of their existence, frequency and importance. The present study, therefore, concerns itself with the morbidity as well as mortality in diabetics. These statistics are published with the view to making the data from an institution with a comparatively large diabetic population available for comparative studies.

One gauge for the estimation of morbidity is a study of the admissions of diabetics to a general hospital. The hospital records of all diabetic patients admitted to this hospital were reviewed for the period from 1933 to 1939. This 7-year period was chosen because it represented approximately 1000 diabetic patients, the exact number being 997. Some of these patients were admitted more than once during this time interval, bringing the total number of admissions to 1164. Of this number of diabetics 436 were males and 661 were females. For comparison, the total of admissions to this hospital, for all causes, in this period of time was 91,100.

An analysis of the age groups of the diabetic patients admitted, reveals the following:

10 years and under	16	41 to 50 years	202
11 to 20 years	39	51 to 60 years	280
21 to 30 years	31	61 to 70 years	294
31 to 40 years	65	71 to 80 years	70

The sudden rise in incidence over the age of 40 parallels the incidence of diabetes by age groups in the general population.

During this 7-year period there were 193 deaths in this group of patients, an approximate mortality rate of 17.5%. One hundred and thirteen postmortem examinations were performed, an average of 58.5%. This relatively high percentage of postmortems is largely due to the interest and coöperation of the house staff.

Tabulation of the discharge diagnoses is given in Table 1. There are certain very definite lessons to be learned from this computation. One is that the acute infections still account for a large percentage of admissions of diabetic patients to the hospital. This perhaps may seem strange in view of the effectiveness of modern therapy in controlling the clinical symptomatology of diabetes.

TABLE 1.—DISCHARGE DIAGNOSES.

Complications.	Times diagnosis was made.	Complications.	Times diagnosis was made.
<i>Vascular Disease</i>	628	<i>Benign:</i>	
Hypertension	163	Uterine fibroids	16
Gangrene	106	Adenoma of bronchus	2
Coronary thrombosis	89	Neurofibromatosis	2
Congestive heart failure	81	Acoustic neuroma	1
Retinopathy	80	<i>Infections</i>	407
Amputations for gangrene	55	Abscess	127
Cerebral thrombosis and hemor- rhage	27	Bronchopneumonia (chiefly termi- nal)	70
Glomerulonephritis	15	Sepsis	33
Pulmonary embolism	10	Tuberculosis	32
Thromboangiitis obliterans	1	Pyelonephritis	22
Paroxysmal tachycardia	1	Lobar pneumonia	21
<i>Gastro-intestinal</i>	146	Acute otitis media and mastoiditis	20
Gall bladder disease	82	Acute sinusitis	17
Cholecystectomy	24	Appendicitis	12
Peptic ulcer	18	Lung abscess	11
Cirrhosis of liver	8	Erysipelas	10
Acute hepatitis	6	Acute upper respiratory infection	10
Colitis	3	Thrombophlebitis	10
Intestinal obstruction	2	Acute pancreatitis	6
Pancreatic cyst	2	Empyema	2
Gastrectomy	1	Vincent's angina	2
<i>Genito-urinary Diseases</i>	85	Meningococcus meningitis	1
Prostatectomy	25	Acute salpingitis	1
Cystorectocoele	16	<i>Coma and Kelosis</i>	201
Uremia	16	<i>Allergy:</i>	
Renal calculi	13	Asthma	8
Cystitis	8	Angioneurotic edema	2
Vesical calculi	6	<i>Skin Diseases:</i>	
Tuberculous kidney	1	Psoriasis	6
Amyloid kidney	1	Vulvitis	5
<i>Hematologic Diseases</i>	36	Herpes zoster	1
Secondary anemia	20	<i>Minor Surgery:</i>	
Leukemia	4	Foreign body (needle)	5
Polyeythemia	4	Tooth extraction	5
Pernicious anemia	4	Fistula in ano	3
Hodgkin's disease	2	<i>Neurologic:</i>	
Agranulocytosis	1	Amyotrophic lateral sclerosis	1
Gaucher's disease	1	Myasthenia gravis	1
<i>Endocrine Disturbances</i>	46	Ménière's disease	2
Hyperthyroidism	44	<i>Miscellaneous:</i>	
Pheochromocytoma	1	Lues	33
Cushing's syndrome	1	Cataract operations	41
<i>Neoplasms:</i>		Rheumatic heart disease	18
Malignant:		Fractures	15
Carcinoma	63	Acute alcoholism	3
		Strangulated hernia	3
		Boeck's sarcoid	1

TABLE 2.—PRINCIPAL CAUSES OF DEATH IN 193 CASES.

	With- out coma.	With coma.		With- out coma.	With coma.
<i>Infection:</i>			<i>Infection:</i>		
Otitis media purulent acute		1	<i>Miscellaneous</i>		9
Acute mastoiditis with sep- sis	3		Consisting of one case each of: postop. acoustic neuroma, leukemia, agranu- locytosis, Hodgkin's, lymphosarco- matosis, hemochromatosis, pheo- chromocytoma, air embolism, un- known.		
Mediastinitis	2		Unknown with coma		2
Carbuncle with sepsis	4		<i>Cardiovascular:</i>		
Acute bacterial endocardi- tis	2		Acute coronary occlusion	39	1
Appendicitis	6		Congestive cardiac failure	23	
Meningitis	1		Gangrene of foot with sep- sis	3	1
Acute pancreatitis		1	Postop. amputation for gangrene	18	
One case each of: acute sinusitis with sepsis, retropharyngeal abscess, can- crum oris, pyarthrosis with sepsis, decubitus ulcer with sepsis, tenosyn- ovitis with sepsis, cellulitis with sep- sis; peritonitis following: volvulus, perforated colonic ca., perforated uterine ca., and perforated duodenal ulcer; acute cholecystitis, acute cholecystitis with sepsis, ca. gall bladder, subphrenic abscess.			Postop. amputation for gangrene and bronchopn.	1	
Pylonephritis	7		Postop. amputation for gangrene and coronary occlusion	2	
Cystitis with sepsis	1		Cerebrovascular accident	6	
Pyonephrosis with sepsis	1		Pulmonary embolism	2	
<i>Genito-urinary:</i>			<i>Pulmonary:</i>		
Uremia	3		Lobar pneumonia	9	
Postop. nephrolithotomy	1		Bronchopneumonia	5	2
Postop. cystolithotomy	1		Lung abscess	3	2
<i>Gastro-intestinal</i>		7	Pulmonary edema	1	
Consisting of one case each of: colonic ca. with metastasis, postop. rectal ca., postop. colonic ca., strangulated femoral hernia, cirrhosis of liver, cir- rhosis with hemorrhage, gastro-intes- tinal bleeding—cause?			Carcinoma bronchus and metastasis	1	
			Pulmonary tuberculosis	3	
			Disseminated tuberculosis	1	
			Pyopneumothorax	2	

TABLE 3.—NECROPSY FINDINGS IN 113 POSTMORTEM EXAMINATIONS.

<i>Cardiovascular:</i>		<i>Endocrine:</i>	
Arteriosclerosis	78	Thyroid adenoma	8
Coronary sclerosis	64	Colloid goiter	3
Acute coronary occlusion	23	Hyperplastic thyroid	1
Old coronary occlusion	8	Atrophy of thyroid	1
Congestive heart failure	16	Cortical adenoma of adrenal	8
Rheumatic endocarditis	15	Cortical hyperplasia of adrenal	2
Hydrothorax	13	Pheochromocytoma	1
Enlarged heart	8	Aplastic testis	3
Bacterial endocarditis	3	<i>Liter:</i>	
Acute pericarditis	2	Chronic passive congest-ion	20
Cerebral thrombosis	5	Cirrhosis	8
Patent foramen ovale	4	Fatty infiltration	15
Calcified aortic stenosis	2	Hepatic artery thrombosis and infarction	4
Myocardial fibrosis	11	Hepatic abscess	1
Miscellaneous	7	Hepatitis	1
One case each of: calcified mitral valve, air embolism, saddle em- bolus of aorta, iliac vein throm- bosis, portal vein thrombosis, hepatic vein thrombosis, fem- oral artery thrombosis.		Hemochromatosis	1

TABLE 3.—NECROPSY FINDINGS IN 113 POSTMORTEM EXAMINATIONS.
(Continued.)

<i>Gall Bladder:</i>		<i>Gastro-intestinal:</i>	
Acute cholecystitis	3	Gastric ulcer	5
Chronic cholecystitis	17	Acute gastritis	4
Cholelithiasis	3	Erosions of stomach	3
Cholesterol infiltration	2	Gastric ca.	1
Cholelithiasis	19	Gastric myoma	3
Spontaneous choledochoduodenos- tomy	1	Gastro-jejunal ulcer	1
<i>Chest:</i>		Duodenal ulcer	6
Lobar pneumonia	4	Duodenal ulcer perforated	1
Bronchopneumonia	43	Intestinal obstruction	3
Pulmonary edema	29	Ileocejunitis	3
Pleurisy with effusion	2	Ulcerative colitis	2
Pulmonary embolism	12	Ca. of colon	4
Bronchicetasis	4	Ca. of rectum	1
Embolie abscesses	1	Colonic diverticulæ	4
Bronchopleural fistula	1	Colonic polyposis	9
Mediastinitis	2	Acute appendicitis	5
Bronchogenic carcinoma	1	Peritonitis	6
Lung abscess	3	Ascites	4
Pyopneumothorax	2	Meckel's diverticulum	2
Tuberculosis	53	Miscellaneous	5
(Primary, 17; disseminated, 7; caseous, 7; fibrotic, 9; cavitation, 3; calcified nodes, 9; exudative, 1.)		One case each of: cancerum oris, peptic ulcer esophagus, esoph- ageal varices, duodenal erosions, chyloma of jejunum.	
<i>Spleen and Blood:</i>		<i>Pancreas:</i>	
Infarcts	7	Lipomatosis	26
Septic spleen	13	Fibrosis	5
Miscellaneous	7	Hyalinized islets	2
One case each of: thrombosis splenic vein, Hodgkin's, aleu- kemic myelosis, tuberculosis, cal- cified aneurysm splenic artery, atrophy, lymphosarcomatosis.		Chronic pancreatitis	1
<i>Neurologic:</i>		Subacute pancreatitis	1
Brain tumor	1	Pancreatic cyst	1
Tabes dorsalis	1	Fat necrosis	2
<i>Miscellaneous:</i>		Atrophy	7
Fractured femur	2	<i>Genitalia:</i>	
Persistent thymus	1	Fibroids	4
<i>Infections:</i>		Ovarian cyst	1
Sepsis	17	Tubo-ovarian abscess	3
Acute otitis media	2	<i>Bladder:</i>	
Lateral sinus thrombosis	1	Cystitis	13
Acute mastoiditis	2	Diverticulum	1
Carbuncle	3	Carcinoma	1
Cellulitis of foot	2	Calculus	1
Gangrene with amputation	11	<i>Prostate:</i>	
Gangrene without amputation	1	Hypertrophy	8
Meningitis	1	Carcinoma	1
Alveolar abscess	1	Thrombosis peri-prostatic plexus	2
Cellulitis of abdominal wall	2	<i>Kidneys:</i>	
Cellulitis of stump	6	Nephrosclerosis	12
Miscellaneous	6	(Glomerulonephritis, 0)	
One case each of: metastatic brain abscess, tenosynovitis (acute), subphrenic abscess, pyo- arthrosis, brain abscess, cellulitis of neck.		Pyelitis	15
		Cortical abscess	1
		Calculi	3
		Renal vein thrombosis	1
		Infarctosis	4
		Miscellaneous	3
		One case each of: amyloid, Kim- melsteil, hypernephroma.	

The degenerative diseases such as arteriosclerosis, gangrene, retinitis, coronary artery occlusion, and cataract, account for the largest percentage of admissions. This perhaps can be partially explained by the preponderance of the old age group in the hospital admissions; the group above 61 years alone comprising half the total admitted. This group also accounted in the main for the malignant neoplasms, terminal bronchopneumonias, sepsis, uremia, and cerebral accidents.

The well-known frequency of staphylococci infections of the skin is borne out by the large number recorded in this series. Yet, on the other hand, the incidence of erysipelas was low. The finding of tuberculosis was usually incidental, for it was most often inactive. Few active cases were observed since the rules of admission precluded their entry into the hospital's general wards. The singular frequency of mastoiditis due to the pneumococcus Type III is to be noted and a detailed report of this association is forthcoming.

The low incidence of admissions for upper respiratory infections and acute sinusitis is due to the fact that hospitalization was advised only in the presence of ketosis.

Lung abscess seemed to be more common in diabetic than in non-diabetic patients in this hospital.

The expected high incidence of gall bladder disease was observed in this group because of the preponderance of females in the middle age or elderly group. An unexpected finding was the number of patients with peptic ulcer, an incidence more than twice that reported by Joslin.

Hyperthyroidism with true diabetes mellitus comprised the largest group of associated endocrine diseases, a finding needing no discussion.

Two conditions not included in this study were arthritis and neuritis. The omission was purposeful in view of the variability of the diagnostic criteria.

Table 2 presents the compilation of the principal causes of death in this series of patients. Only the most important conditions which actually precipitated the death of the patient is reported in this table. The outstanding finding is the number of deaths attributed to cardio-vascular disturbances, the actual percentage being 48.6%. This can be correlated with the fact that 55.4% of patients admitted showed clinical evidence of cardio-vascular disease.

The next important group is the infections which accounted for 23.3% of the mortalities. This does not include pulmonary infections. If the latter be included, the figure rises to 37.3%. The high mortality is undoubtedly related to the fact that hospitalization is restricted to those infections which can no longer be treated on an ambulatory basis. These figures are "weighted" by the high mortality rate in lung abscess, lobar pneumonia, and sepsis. On the other hand, infections such as abscesses including carbuncles, which

are amenable to surgery, by virtue of the availability of insulin therapy, showed a much lower mortality, namely 8.6%.

In Table 3 are listed the autopsy findings in 113 patients. These are published merely to show the excellent agreement of our findings with those previously reported.

Summary. The data presented show that in spite of the availability of insulin therapy, the diabetic still presents the same complications as he has in the past.

THE INCIDENCE OF TRICHINOSIS IN NEW YORK CITY.*

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THE incidence of human infestation by *Trichinella spiralis* has received widespread publicity in recent years both in lay and scientific reading matter. The range in the figures reported varies from 3.5⁴ to 36%² from various parts of the United States (Ann Arbor, Detroit, Cleveland, Louisiana), with a probable average incidence of about 17% throughout the country. This latter estimate is based on a comprehensive study of over 3000 human diaphragms obtained at necropsy from a widespread area of the country and reported by the National Institute of Health.⁵ In several recent papers on the incidence of trichinosis all the previous incidence studies are summarized in tabular form.^{1,3}

The present study was undertaken in order to discover the incidence of human infestation with *T. spiralis* in New York City by the use of a combination of digestion, press, and histologic methods on autopsy material, and to evaluate the relative efficacy of these methods to detect the presence of infestation.

Material. The muscles taken for study were removed from bodies selected at random daily from the large number of cases necropsied by the Office of the Chief Medical Examiner in the Borough of Manhattan. These necropsies were carried out on cases of homicidal, suicidal and accidental deaths, deaths from poisoning, drowning and other types of asphyxia, also sudden and unexpected deaths from natural causes. Only bodies of adults

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in a good state of preservation were utilized as a source of material. No attempt to select cases on the basis of age, sex, race, nationality, religion, economic status, or diagnosis was made. No known case of trichinosis was included in this series. The cases necropsied by the Office of the Chief Medical Examiner are a representative sample of the various racial strains and the economic levels of the population of New York City. A total of 100 cases was investigated: 83 males and 17 females; 79 were white, 29 black. The ages varied between 17 and 74 years, with 30 cases in the fourth decade, 25 in the fifth and 39 in the sixth decades.

Liberal samples of material (approximately 25 gm. from each site) were removed from each diaphragm, the intercostal, pectoral and psoas muscles, and placed in separate Petri dishes for study by the methods described below. Six samples were obtained from each case.

Methods. 1. *Examination by Press.* About 2 gm. of each muscle sample from each case were cut into small fragments and examined directly in a special press* through a binocular microscope (3.2 and 10x objectives, 10x oculars). Each specimen was examined systematically and if parasites were found the number of larvæ or cysts recorded. In addition, a piece of diaphragm, 2 by 2 cm. was stripped of its membranes and examined *in toto* in the press.

2. *Histologic Examination of Formalin Fixed Tissue.* Blocks of muscle from each of the samples used for digestion were fixed in 10% formalin and embedded in parlodion. Sections were cut 10 μ thick and approximately every tenth section was selected for staining with hematoxylin and eosin. Five to 10 sections were stained from each of 6 blocks in each case making a total of from 30 to 60 sections from the 6 muscle sites. The muscle fibers were sectioned longitudinally and a large area of muscle, approximately $\frac{3}{8}$ inch square, was available for histologic examination.

3. *Digestion.* A combined total of 50 gm. of muscle selected from 6 of the sites described, including the diaphragm in all cases, was used for digestion. The material was finely chopped or ground and placed in a 2 liter beaker containing 1000 cc. of digestion fluid (5 G pepsin, 7 cc. hydrochloric acid, Sp. gr. 1.19, 1000 cc. tap water). The mixture is incubated at 37° C. for 18 to 24 hours and stirred frequently. When removed from the incubator the beaker is allowed to stand for 15 to 20 minutes. The supernatant fluid is carefully drawn off by suction until the fluid level is 1½ inches from the bottom, leaving about 450 cc. The remaining mixture is then filtered through a single layer of cheese cloth (mesh 20-22) into a 450 cc. cylinder, 2 inches in diameter and 12 inches in height. It is allowed to settle 30 to 45 minutes and the supernatant liquid drawn off by suction until the fluid level is 3 inches from the bottom leaving about 100 cc. in the cylinder. The latter is now mixed with warm water which is added until the cylinder is full. This washes the sediment and floats particles of fat, muscle, and connective tissue to the top. The mixture is allowed to stand 30 to 45 minutes and the supernatant liquid again carefully removed by suction until the fluid level is 3 inches from the bottom, leaving about 100 cc. in the cylinder. The remaining mixture is transferred to two 50 cc. conical centrifuge tubes and centrifuged at 1000 R.P.M. for 3 minutes. The supernatant fluid is again drawn off by hand using a bulb and pipette, leaving 2 cc. of suspended sediment at the bottom of each centrifuge tube. This entire suspension is then examined microscopically drop by drop on a

* Two brass plates, each 3½ by 3½ by ½ inches, with the center cut out as a circle 2½ inches in diameter, countersunk ½ inch and recessed ¼ inch, are used as frames to hold together two plates of glass, each 2½ inches in diameter and ¼ inch thick. Eight set screws ½ inch diameter and ½ inch long are fixed in one of the plates around the circular cut-out about ¼ inch from its edge. The other plate is appropriately drilled to permit the screws to pass through it freely. Both plates and glass are lapped and pressed together with wing nuts.

large slide ($1\frac{1}{2}$ by 3 inches) using a mechanical stage and binocular microscope (3.2 and 10x objectives and 10x oculars). If positive, the number of larvæ or cysts is recorded.

Results. In 100 cases studied, there were 22 that were positive for trichinæ by all methods combined, or an incidence of infestation by *T. spiralis* of 22% in this series of violent and sudden deaths in New York City. In the tables below (Tables 1 to 4), the results obtained in this study are presented and analyzed. Typical findings in a positive case are illustrated in Fig. 1 (A to D).

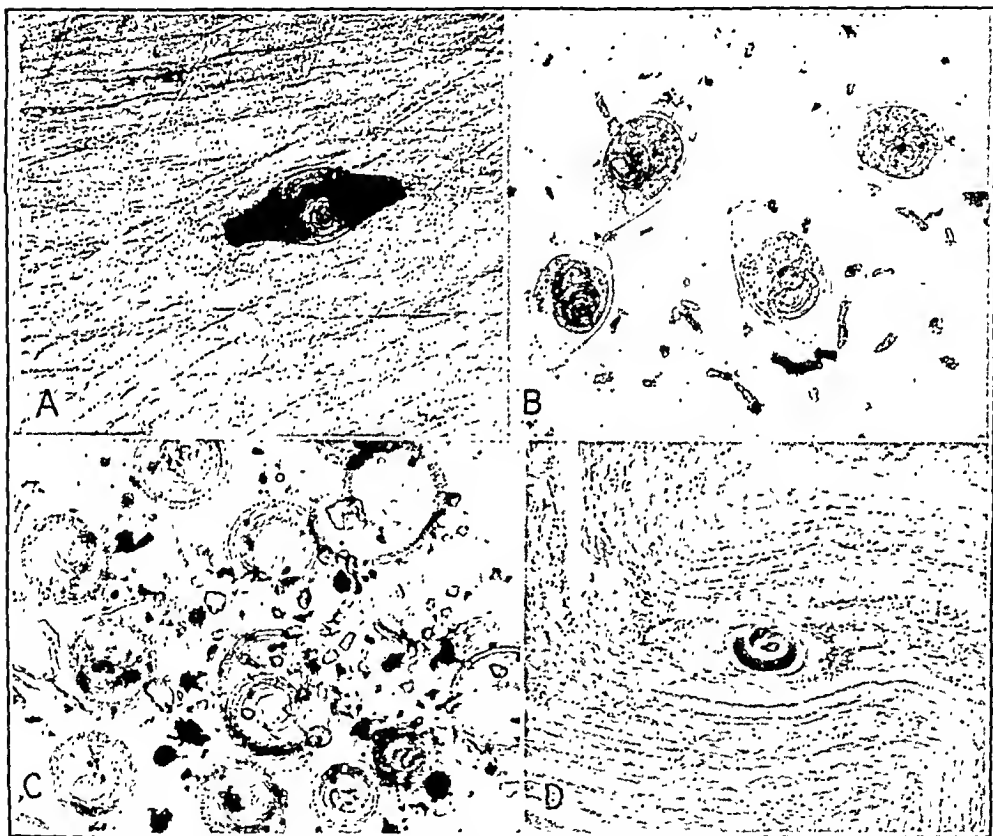


FIG. 1.—Findings in a positive case of infestation by *Trichinella spiralis*. A, Press preparation, encysted larva showing bipolar calcification, 16 mm. objective. B, Digestion, washed sediment. Encysted larvæ of *T. spiralis*, 16 mm. objective. C, Digestion, washed sediment. Completely freed young living larvæ of *T. spiralis*, 16 mm. objective. D, Histologic section. Encysted parasite. Focal myositis, 16 mm. objective. (Hematoxylin and eosin stain.)

Comments. *Press Method.* Eight cases of the entire series were positive for trichinæ by this method or an incidence of only 8% if this method alone had been employed. These 8 positive cases obtained by press represent 36.3% of the entire 22 positives in the series. All of the cases positive by press were also positive by digestion and in addition, 7 of them were positive by the histologic section method. Only 1 of the positive press cases was negative by his-

TABLE 1.—ANALYSIS OF POSITIVE CASES.

Case No.	Press.			Digestion, larvae per 50 gm. muscle.	Histologic examination.				
	Pect.	Dia.	Psoas.		Total sections.	Blocks, pos.	Slides, pos.	Total parasites.	Myositis.
2	0	0	0	0	50	1	4	4	+
3	0	0	0	1	52	0	0	0	+
14	0	0	0	6	35	0	0	0	+
18	0	2	0	3	50	1	1	1	+
20	0	4	0	13	39	3	3	3	—
22	1	3	2	143	30	3	8	12	+
27	0	1	0	16	36	0	0	0	+
29	0	2	0	25	50	3	10	10	+
35	0	0	0	14	40	1	2	2	+
36	14	78	6	760	60	6	60	500	+
40	0	0	0	7	26	0	0	0	—
41	0	0	0	2	26	0	0	0	—
56	0	0	0	2	36	0	0	0	+
59	0	6	0	63	36	1	3	3	+
60	0	0	0	6	35	0	0	0	+
66	0	0	0	7	32	0	0	0	—
68	0	0	0	31	31	2	3	3	+
71	0	0	0	1	24	0	0	0	—
77	0	0	0	6	30	0	0	0	—
80	0	0	0	9	38	0	0	0	+
93	0	0	0	21	36	2	6	6	+
97	2	12	0	310	24	4	10	12	+

TABLE 2.—COMPARISON OF RESULTS BY VARIOUS METHODS, 100 CASES.

Method.	No. positive.	Per cent.
Press	8	8
Digestion	21	21
Histologic section	11	11
All methods combined	22	22

TABLE 3.—DEGREE OF INFESTATION (DIGESTION).

Larvæ per 50 gm.	No. of cases.
1-10	11
11-50	6
51-100	1
101 and above	3

TABLE 4.—AGE, SEX, COLOR AND CAUSE OF DEATH IN 22 POSITIVE CASES OF TRICHINELLA INFESTATION.

Case No.	Age.	Sex.	Color.	Cause of death.
2	33	F	W	Fractured skull
3	65	M	W	Fractured skull
14	35	M	W	Alcoholism
18	50	M	W	Heart disease
20	46	M	W	Bullet wound
22	30	M	B	Heart disease
27	39	M	W	Alcoholism
29	64	M	W	Heart disease
35	42	M	B	Fractured skull
36	32	F	B	Ruptured aneurysm
40	37	F	B	Alcoholism
41	27	F	B	Stab wound
56	32	F	B	Cerebral hemorrhage
59	59	M	W	Heart disease
60	42	M	W	Fractured skull
66	36	M	B	Nitric acid poisoning
68	72	M	W	Multiple injuries
71	61	M	W	Fractured skull
77	42	M	W	Alcoholism
80	39	M	B	Alcoholism
93	31	M	W	Cerebral hemorrhage
97	38	M	W	Heart disease

tologic section. Five of the 8 press positives revealed larvæ only in the diaphragms, while in the 3 remaining cases, larvæ were found in the pectoral, psoas, and intercostal muscles as well as in the diaphragms. Apparently, the press method alone cannot be utilized in evaluating the degree of infestation, if one compares the results obtained by this method with those obtained by digestion. Since the press method would probably reveal only about one-third of the positive cases in any series studied, it cannot be relied on solely in any incidence study. Nevertheless, since press examination is a very simple procedure and since the muscle utilized can be submitted subsequently to digestion, it is suggested that this method be employed routinely in the preliminary examination of biopsy material for the diagnosis of trichinosis. It must be appreciated, however, that the press examination of the usual small specimen removed at biopsy from a single muscle may be negative for trichinæ, even though there is strong clinical evidence to support the diagnosis of trichinosis.

An interesting observation was noted during press examinations of several of the positive diaphragms. Occasionally, old, calcified, dead trichinæ cysts as well as young, viable larvæ, were found in the same specimen. This would indicate that reinfection in man does occur.

Digestion. Of the 22 positive cases in the entire series 21 were positive by digestion. Thus digestion alone would have detected 95.4% of all the positives in the series and would have yielded an incidence of 21% for the whole study or only 1% less than the final incidence obtained as a result of all the methods combined.

Ten of the 22 positive cases were detected by digestion alone and not by the 2 other methods employed. It is noteworthy that in the cases detected by digestion alone there were less than 10 larvæ per gram of muscle. Apparently digestion is of great value in discovering light infections, though, to be sure, the percentage of positives would be much less if smaller amounts of tissue were taken for digestion. Without digestion, the incidence in this series would have been only 12%. The digestion method detected 13 more positive cases than did the press method and 10 more than were found by the histologic method.

It seems desirable therefore to include digestion studies in any survey which aims to detect the highest possible incidence of trichinosis in postmortem material. The digestion technique can be safely employed alone utilizing moderate amounts of diaphragm with reasonable certainty that a fairly true estimate of the incidence of trichinosis would be revealed in a postmortem survey.

From the standpoint of laboratory diagnosis of trichinosis on biopsy material, digestion should be carried out even though other methods are unsuccessful. It has been our experience in many cases to find larvæ by digestion when press and histologic examinations

were negative. Digestion of the small amount of muscle usually obtained by biopsy is a very simple procedure and can be carried out in any laboratory. The muscle tissue obtained at biopsy may be treated in the following manner: A very small sample of the biopsy is placed in formalin for histologic study which may reveal a suggestive myositis even though the parasites are not found. The remainder of the specimen is then examined by press and if this examination is negative, by digestion. If one is interested in correlating the clinical severity of the disease with the number of larvæ in each gram of muscle, the specimen is weighed and submitted to digestion, so that the total number of larvæ or cysts in it can be counted.

In the present series only 1 of the positive cases was negative by digestion. In this case only 1 parasite was found in the diaphragm in 1 out of a total of 50 histologic sections prepared from 6 blocks of tissue.

In several cases showing the severest degree of infestation, attempts to demonstrate larvæ in the heart muscle were unsuccessful.

Histologic Method. Approximately 4000 histologic sections were examined in this study and in 11 cases parasites were detected. Thus only half of the final total of 22% would have been obtained had this method alone been used. It is noteworthy that of the 600 blocks from which 4000 sections were cut in the entire series, only 4.5% of the blocks and 2.7% of the sections were found to contain parasites. Of the 22 cases positive by all methods, only 20% of the blocks and 13.4% of the slides were positive and of the 11 positive cases discovered histologically, 40% of the blocks and only 25% of the sections cut from them were found to contain parasites.

Histologic examination did detect 4 positive cases which were negative by press including 1 which was also negative by digestion. The case detected histologically and not by digestion would have changed the final total incidence of infestation by only 1% if it had not been discovered. Inspection of Table 1 reveals a serious drawback in the value of the histologic method in that it fails in most cases to detect infections which yield less than 10 larvæ per 50 gm. of muscle by digestion.

Interstitial focal myositis was noted in most of the positive cases. In some sections in which parasites were not found the myositis was so intense as to suggest that if more or the next sections had been examined, parasites would have been found. Myositis was also observed in some cases which were negative by all the methods and it was absent in several of the milder infections.

The histologic examinations carried out in this study were time consuming and laborious. Only half the positive cases in this series were confirmed by this method and in these positive cases parasites were found in relatively few sections out of the large number exam-

ined. The histologic method used alone in any survey is therefore unreliable and impractical. The rare positive case which might be discovered by histologic examination and missed by press or digestion, hardly justifies the inclusion of this method with the other methods in any postmortem incidence study.

In the laboratory diagnosis of trichinosis on biopsy material it must be emphasized again that unless the infection is very heavy and widespread, the likelihood of finding parasites in a few slides from a random block of a single muscle is small. Often in a clear-cut clinical case of trichinosis the histologic examination of the biopsied muscle fails to reveal any parasites, although it may reveal a suggestive myositis.

Summary and Conclusions. 1. In a series of 100 bodies of persons dying by violence or suddenly from natural causes in New York City, studied by a combination of press, digestion and histologic methods, there were 22 cases of infestation by *T. spiralis*, an incidence of 22%. This would suggest that the occurrence of human trichinosis in New York City is considerable and well beyond clinical appreciation and recognition of the disease.

2. Digestion of large amounts of muscle, preferably the diaphragm, is the most feasible and reliable method to determine the incidence of infestation in man and will detect the largest number of positive cases in contrast to other methods, especially if the infestation is light.

3. The relative efficacy in detecting positive cases of infestation in this series by the methods of digestion, histologic examination and press was in the ratio of 21 to 11 to 8, respectively. Without the use of the digestion method the incidence determined in this series would have been 12%.

4. In addition to routine histologic examination, muscle obtained by biopsy for diagnosis should be studied routinely by press and then submitted to digestion to determine the number of larvæ per gram of muscle. The procedures are simple and can be performed in any laboratory. They will reveal more positive cases of infestation than the method of histologic examination used alone. Random histologic sections from a single small block of biopsied muscle will frequently be negative despite strong clinical and laboratory evidence of trichinosis.

5. Reinfection in man by *T. spiralis* does occur.

We wish to acknowledge with thanks the technical assistance of Ethyl Greenwald Ringer, A.B., and Morris Kolin, B.S.

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NEGATIVE THERAPEUTIC AND METABOLIC EFFECTS OF SYNTHETIC ALPHA-TOCOPHEROL (VITAMIN E) IN MUSCULAR DYSTROPHY.

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IN 1922 Evans and Bishop,⁴ and later others, reported on the existence of a dietary constituent which was essential for normal reproduction in the rat. This substance was subsequently known as vitamin E. In later work Evans, his coworkers and others found that suckling rats born of mothers which had received a diet low in vitamin E developed paralysis of the skeletal musculature and a large number soon died. This occurred in spite of the fact that the mothers produced adequate amounts of milk for normal growth. The pathology of this experimental form of muscular paralysis has been reported to be associated with lesions of the nervous system by some investigators^{3,12} but this has been denied by others.^{2,7,8,15,16} These paralyzes could be prevented by the administration of substances rich in vitamin E as late as the 15th day of life.

Subsequent investigators^{6,8,13} were able to show that alpha-tocopherol was effective in curing or preventing the development of this experimental form of nutritional muscular dystrophy and more recently Knowlton, Hines and Brinkhous¹¹ reported that synthetic alpha-tocopherol acetate was efficacious in the cure and prevention of the experimental muscular dystrophy produced by vitamin E deficiency.

Owing to the reports of Bicknell¹ and of Stone¹⁷ on the efficacy of vitamin E in the form of wheat germ oil or dried wheat germ in the treatment of some cases of muscular dystrophy and of atrophy, this study regarding the therapeutic and metabolic effect of synthetic *dl*-alpha-tocopherol acetate* in muscular dystrophy was undertaken. Such study was especially indicated because of the possibility, as some of the investigators^{8,14} had pointed out, that other essential factors besides vitamin E might be present in the crude wheat germ oil extract which might be responsible for the therapeutic effect.

Procedure. A group of 5 cases of progressive muscular dystrophy, 4 male and 1 female, was chosen for this study, which was made entirely in 1940. These cases had been under our observation for from 2 to 7 years and the general clinical course of the condition was well known in each case. It will be noted from the protocols that 2 of the male patients (Cases 1 and 3) had older brothers who

* Synthetic *dl*-alpha-tocopherol acetate was used throughout this study. It was kindly supplied, in part, by Hoffmann-La-Roche, Inc.

also had progressive muscular dystrophy. The female patient (Case 4) was of especial interest because her muscular weakness became manifest for the first time during a pregnancy.

The patients were placed on meat-free, low-purine diets for several days prior to treatment and total 24-hour specimens of urine were collected daily during this fore period. The patients were then permitted to eat a regular mixed diet and *dl*-alpha-tocopherol acetate was administered orally in increasing doses of from 9 mg. to 200 mg. daily for varying periods of from approximately 3 to 6 months as indicated in the protocols. At intervals of 1 to 2 weeks during the course of treatment and after treatment the patients were put on a meat-free diet for 2 consecutive days and total 24-hour specimens of urine were collected on these days. The creatinine and creatine in each 24-hour specimen of urine was determined quantitatively. The Folin method was used as adapted by Kassell¹⁰ for the Pulfrich photometer.

Clinical Histories.—CASE 1. J. B., a male, age 9 years, was seen for the first time in 1938, at the age of 7, because of peculiar gait and some difficulty in climbing stairs. His brother also had suffered from progressive pseudohypertrophic muscular dystrophy and had been seen by us since 1933; he died in 1940 at the age of 15 years at which time he was totally incapacitated. The patient in 1933 was 18 months old and was reported to be walking, and apparently well. The rest of the family history as regards grandparents, maternal and paternal aunts and uncles and a sister was negative as to relevant illness.

Physical Examination. On March 9, 1940, before treatment, the patient showed involvement of upper and lower extremities. He walked with a shuffling and waddling gait and marked lordosis. He could not climb stairs. The power for flexion and extension at the elbow joints was weak; flexion of thighs on hips was very weak. There was some bilateral weakness of the quadriceps femoris muscles; dorsiflexion of both feet was limited in extent; plantar flexion was very strong and the calf muscles appeared hypertrophied. There were no fibrillary twitchings of the skeletal musculature; no sensory disturbances. The knee jerks, biceps and triceps reflexes were absent. The ankle jerks were active. The genitalia were somewhat hypoplastic, the testes being small and soft. The rest of the physical examination was negative.

Alpha-tocopherol Treatment. March 21 to April 6—3 mg. t.i.d. = 9 mg. daily.

April 6 to May 26—6 mg. t.i.d. = 18 mg. daily.

May 26 to May 31—9 mg. 4.i.d. = 36 mg. daily.

June 1 to Sept. 26—20 mg., 10 mg., and 20 mg. = 50 mg. daily.

Oct. 5 to Oct. 26—50 mg. 4.i.d. = 200 mg. daily.

Course. Since April 5, the family was of the opinion that the patient had more power in his upper extremities. They stated he could lift some heavy toys which he did not do before. Physical examination, however, failed to reveal any notable changes. The patient is still under observation (March, 1941) with condition essentially unchanged.

The metabolic changes are seen in Table 1.

CASE 2.—M. Y., male, aged 14, had been under our observation because of difficulty in walking since 1933 when he was 3 years, 8 months old. His birth was normal. He was a bottle fed infant and did not present any feeding problem except between 2½ and 3½ years of age, at which time he had

frequent attacks of vomiting. He started to walk at 19 months of age. The family history was negative for any relevant illness. The patient was an only child of a second marriage. His father had had 3 children, 1 boy and 2 girls by the first wife. These children were all well. The patient had grown progressively worse during the past 7 years with involvement of both upper and lower extremities.

Physical Examination. The patient was still ambulatory at the time of the examination just prior to treatment with alpha-tocopherol. There was marked weakness in abduction of arms and in flexion and extension of forearms. The grip of both hands was weak but there was no atrophy of the interosseous muscles. The lower extremities showed marked weakness in flexion of thighs on hips and in extension of the legs. Dorsiflexion of feet was weak while plantar flexion was very good. There was marked lordosis of the lumbar spine. The knee jerks, biceps and triceps, tendon reflexes could not be elicited. The ankle jerks were present. The patient rose from the sitting position with great difficulty. Genitals appeared hypoplastic and pubic hair was just making its appearance.

Alpha-tocopherol Treatment. April 13 to June 1—6 mg. t.i.d. = 18 mg. daily.

June 1 to Sept. 7—20 mg., 10 mg. and 20 mg. = 50 mg. daily.

Sept. 14 to Sept. 28—20 mg., 10 mg. and 20 mg. = 50 mg. daily.

Sept. 28 to Oct. 10—No treatment.

Oct. 10 to Nov. 2—50 mg. alpha-tocopherol, 4 i.d. = 200 mg. daily.

Course. The parents of the child were of the opinion that his upper extremities were somewhat stronger as a result of the treatment. The physical examinations, however, failed to reveal any notable change. The patient is still under observation (March, 1941) with condition essentially unchanged.

CASE 3. M. T., male, aged 19, was first seen by us in 1933 at the age of 12. At that time the chief complaint was difficulty in walking up the stairs. His birth was normal. He was breast fed and as a baby had frequent colds. He began to walk at 13 months and appeared well up to 4 years when he began to have difficulty in walking up the stairs. His condition grew progressively worse and at present, although he is still ambulatory, he has involvement of both upper and lower extremities.

The family history was of interest in that there are 3 sisters who are well and 2 older brothers, 1 of whom, the oldest, was totally incapacitated by muscular dystrophy. The rest of the family history was negative for relevant illness.

Physical Examination. Patient had a marked lordosis and a waddling gait. He rose from the sitting position with great difficulty. The ability to abduct the arms was fairly good. Flexion and extension at the forearms was very weak. The grip in the hands was good. There was some weakness in the power to flex thighs, the hips, and considerable weakness in extension of the legs and dorsiflexion of the feet. Plantar flexion of the feet was very good. The calves of the legs appeared hypertrophic. The knee jerks, biceps and triceps, tendon reflexes could not be elicited. The ankle jerks were active. There were no fibrillary twitchings of the muscles and no sensory disturbances. The external genitals appeared hypoplastic.

Alpha-tocopherol Treatment.—July 6 to Sept. 12—20 mg., 10 mg., 20 mg. = 50 mg. daily.

Sept. 12 to Oct. 3—30 mg., 20 mg., 30 mg., 20 mg. = 100 mg. daily.

Course. Patient showed neither subjective nor objective improvement. He is still under observation (March, 1941) with condition essentially unchanged.

CASE 4.—E. S., male, aged 16, came under our care in 1933 at the age of 10 because of difficulty in walking. Examination at that time showed appreci-

able involvement of both upper and lower extremities. His birth was normal and he was bottle fed and presented no feeding problems. He had chicken-pox, whooping cough and acute otitis media during infancy and childhood. The family history was negative for relevant illness. There were no male siblings and only 1 other sister who was well.

Physical Examination. Patient was practically totally incapacitated presenting a picture of far advanced progressive muscular dystrophy. *Alpha-tocopherol Treatment.* April 11 to June 5—6 mg. t.i.d. = 18 mg. daily.

June 5 to Sept. 30—20 mg., 10 mg., 20 mg. = 50 mg. daily.
Oct. 8 to Nov. 2—50 mg. 4 i.d. = 200 mg. daily.
Course. No notable change occurred as a result of the treatment. The patient is still under observation (March, 1941) with condition essentially unchanged.

CASE 5.—P. B., female, aged 43, married, came to our clinic in 1938 at the age of 41 because of weakness in upper extremities and difficulty in walking. She stated that in 1932, when she was in the second month of pregnancy, she noted that she was developing weakness in her upper extremities and difficulty in climbing stairs and had noted no physical difficulties before that time. However, she went through pregnancy and gave birth to a normal, healthy, female infant, who is now 8 years' old and in excellent health. The patient also noted that she was clumsy in handling the infant. Her condition grew progressively worse although she was still ambulatory at the time of the present investigation. The menstrual period had been normal and there was no history of miscarriages except that of a therapeutic abortion in the second month of pregnancy, subsequent to her first pregnancy. This was done because she felt that the pregnancy was increasing the weakness of her muscles. The family history was negative for any relevant illness.

Physical Examination. Patient had a waddling gait and marked lordosis of the back. She rose from the sitting position with difficulty. Power to abduct the arms was fairly good. There was marked weakness in flexion and extension of the forearms. The grip in both hands was very good. There was appreciable weakness in flexion and extension of the thighs on hips. However, the power for flexion and extension of the legs at the knees and for dorsiflexion and plantar flexion of the feet was very good. (NOTE: The marked weakness usually found in the quadriceps femoris and the tibialis anticus muscles, and previously noted in the 4 male patients, was absent in this case.) There were no sensory disturbances. The knee jerks and ankle jerks were present. The biceps and triceps tendon reflexes could not be elicited.

Alpha-tocopherol Treatment. March 18 to April 14—3 mg. daily.
April 14 to June 6—6 mg. t.i.d. = 18 mg. daily.
June 6 to July 15—20 mg., 10 mg., 20 mg. = 50 mg. daily.
July 15 to Aug. 1—Off treatment (though she felt better while on treatment).

Aug. 1 to Sept. 12—50 mg. daily.
Sept. 12 to Oct. 28—50 mg. 4 i.d. = 200 mg. daily.
Course. As indicated above, the patient thought she was feeling better along toward the middle of her course of treatment. She said she thought she could do things with less stress although she did not think she had any increase in muscular power. Subsequently, however, she felt she was in no better condition and decided to discontinue her treatment completely. On physical examination there appeared to be some slight increase in power in flexion of thighs on hips and also the triceps reflexes could be elicited. She is still under observation (March, 1941) with condition essentially unchanged.

Metabolic Observations. It will be seen from the table that all of the cases had an appreciable creatinuria with rather low preformed creatinine excretions. The patient (Case 4) who was most disabled had the lowest preformed creatinine excretion per day. The preformed creatinine amounted to less than one-third of the "total creatinine"* excretion per day. Only 2 of the cases showed a tendency to a rise, the other cases showed practically no changes or a slight fall in creatinine excretion. The relative creatinuria continued to be marked throughout the period of study.

TABLE 1.—THE EFFECT OF THE ADMINISTRATION OF *dl*-ALPHA-TOCOPHEROL ACETATE (SYNTHETIC) ON CREATININE AND CREATINE EXCRETION IN CASES OF PROGRESSIVE MUSCULAR DYSTROPHY.

Case No.	Period of treatment.	Daily dose (mg.).	Average urinary excretion per day.		
			Preformed creatinine (gm.).	Total creatinine (gm.).	Creatine (gm.).
1	Before treatment	None	0.22	0.62	0.48
	Mar. 21-June 1	9-36	0.23	0.62	0.45
	June 1-Aug. 27	50	0.21	0.60	0.44
	Oct. 5-Oct. 26	200	0.20	0.62	0.47
	Oct. 27-Dec. 14	None	0.23	0.68	0.54
2	Before treatment	None	0.24	0.51	0.38
	April 13-June 1	18	0.25	0.64	0.45
	June 1-Sept. 7	50	0.28	0.71	0.50
	Sept. 14-Sept. 28				
	Oct. 10-Nov. 2	200	0.29	0.66	0.43
3	Nov. 2-Dec. 14	None	0.31	0.72	0.48
	Before treatment	None	0.36	0.76	0.46
	July 6-Sept. 12	50	0.33	0.65	0.38
	Sept. 12-Oct. 4	100	0.30	0.61	0.36
	Oct. 4-Nov. 30	None	0.28	0.54	0.30
4	Before treatment	None	0.16	0.51	0.41
	Apr. 11-June 5	18	0.16	0.52	0.42
	June 5-Sept. 30	50	0.16	0.51	0.41
	Oct. 8-Nov. 2	200	0.14	0.48	0.39
5	Before treatment	None	0.58	1.04	0.52
	Mar. 18-June 6	3-18	0.58	1.07	0.54
	June 6-July 15	50	0.58	1.13	0.65
	Aug. 1-Sept. 12				
	Sept. 12-Oct. 28	200	0.63	1.10	0.56
	Oct. 28-Nov. 15	None	0.58	0.99	0.46

Discussion. It might be expected that any marked improvement in the skeletal musculature of the patients would be associated with a rise in the daily creatinine excretion associated with a decreased tendency to creatinuria. Furthermore, as was reported in a previous publication,⁹ the proteins and the amino acids in the diet may readily affect the level of the abnormal creatine excretion without affecting the creatinine excretion, and this stability of the abnor-

* Total creatinine represents the sum of the preformed creatinine plus the creatine, which is determined as creatinine.

mally low creatinine excretion should render it a better guide to significant changes in the skeletal muscles, although alleviation of creatinuria is also important. It was also pointed out in the aforementioned report that as the muscular dystrophy progressed the creatinine decreased.⁹ These clinical findings regarding creatinine and creatine metabolism differ from those reported by MacKenzie and McCollum¹³ for experimental nutritional muscular dystrophy in animals. These investigators found that as the animals developed muscular dystrophy they also developed a marked creatinuria; however, the creatinine excretion remained practically unaltered. The first sign of therapeutic response in their animals was a drop in creatine excretion without any notable change in creatinine. It is possible that this difference in creatinine metabolism between our patients and the experimental animals may point to some fundamental difference in pathogenesis.

As was indicated previously, only 2 of the cases showed a rise in creatinine excretion. However, in spite of this small rise, the creatinine excretion continued to be abnormally low. The continued low creatinine output and marked creatinuria in all the cases was in keeping with the lack of any marked change in the physical condition of the patients. The slight improvement described by the patients is indicated in the protocols.

The results obtained with *dl*-alpha-tocopherol acetate as compared with those obtained by Bicknell and by Stone in their cases treated with wheat germ oil or dried wheat germ and vitamin B complex, raise several questions, whether the wheat germ preparations which they used contained other essential substances besides vitamin E, whether the added vitamin B complex played any rôle, or whether the types of muscular dystrophy which they treated were different from ours. No metabolic data are given by these investigators which could be used for comparison.

It is hoped that further study of the same clinical material using a therapeutic regimen similar to that of the above investigators may help to elucidate this problem.

Summary and Conclusions. 1. The metabolic and therapeutic effects of synthetic *dl*-alpha-tocopherol acetate in 5 cases (4 male and 1 female) of progressive muscular dystrophy are reported.

2. Two of the male patients had a familial history of the disease.

3. The marked therapeutic effects of wheat germ oil reported by some investigators were not obtained with the use of synthetic vitamin E.

4. Some differences in creatinine metabolism between experimental nutritional muscular dystrophy in animals and muscular dystrophy in man are pointed out.

5. The significance of the findings are discussed and plans for further investigations are indicated.

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ADDISON'S DISEASE: TREATMENT AND PROGNOSIS.

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DURING the past 7 years as various biochemical and physiologic discoveries were made, treatment for Addison's disease has been modified periodically. At the Mayo Clinic, for example, from 1933 to 1935 patients were treated with liberal amounts (10 gm.) of sodium chloride and injections of cortical extract that were prepared by Kendall. During the latter part of this period sodium citrate (5.0 gm.) was administered in conjunction with the sodium chloride. Cortical extract was used during crises and regularly at other times by those patients (the majority) who could not get along without it.

In 1935 a diet that was low in potassium was added as an adjunct to the therapeutic measures previously employed.⁹ After this change had been made it was found that some patients required the use of cortical extract every day; some, only during periods of stress; and others, not at all. It was our clinical impression that patients sustained on this regimen needed less cortical extract, had fewer crises and were more able to carry on normal activities than those whose diet was unrestricted. The low potassium diet, however, required careful preparation and was limited in variety of foods.

In 1939, desoxycorticosterone acetate was made available for clinical use. A series of steroid compounds were isolated almost simultaneously from the adrenal cortex by Kendall and his associates^{1,2,3} and by Reichstein,⁴ shortly thereafter Steiger and Reichstein⁶ synthesized desoxycorticosterone acetate. The powerful effects of this compound on the excretion of sodium, potassium, chloride and urea were appreciated promptly by Thorn,⁷ who first

applied it clinically in the treatment of Addison's disease. Subsequently it was used at the Mayo Clinic and elsewhere.

In the evaluation of the results obtained in the treatment of Addison's disease it is important to bear in mind that prior to the advent of modern substitutional therapy the prognosis was exceedingly grave. Although in very exceptional instances untreated patients and patients treated by measures that would now be regarded as ineffectual lived for as long as 10 years after the onset of symptoms, comparatively few were alive 5 years after the onset of symptoms. It is equally important to remember that treatment for chronic adrenal insufficiency does not cure or arrest tuberculosis and that, even if perfect replacement therapy were available, early death from tuberculosis would occur in an appreciable number of instances. Finally, the prognosis in individual cases of Addison's disease in which the etiologic factor is tuberculosis is unquestionably influenced by the amount of adrenal tissue that has not been destroyed by the tuberculous process. There is no available method at the present time by which the amount of this remnant of healthy cortical tissue can be determined. To make matters more complicated, there is reason to believe that in recent years there have occurred a decrease in the incidence of tuberculosis and an increase in incidence of atrophy as the cause of Addison's disease. If such is the case, the influence on prognosis can only be conjectured. It is evident, therefore, that a mere statistical analysis of survival is unlikely to give a picture that is free from distortion.

In 1938, Rynearson, Snell and Hausner⁵ presented data on 43 cases of Addison's disease in which the patients were examined at the Mayo Clinic between October, 1933, and July, 1937. We wish to present data on 67 additional cases in which the patients were seen between July 1, 1937, and December 31, 1940, inclusive, together with an analysis of therapeutic results that were obtained in both groups.

Of these 110 cases there was evidence of tuberculosis (either active or arrested) involving the lungs, bones, kidneys, genitals or cervical lymph nodes in 37 (34%). It is probably safe to assume that atrophy was the etiologic factor in the majority of the remaining 73 cases. Among the entire group of 110 cases, associated disease that might have influenced mortality* and degree of morbidity was present in 41 cases. These associated diseases included calcareous aortic stenosis, latent syphilis, duodenal ulcer, unexplained fevers, rheumatic endocarditis, migraine, hypertension,† renal calculi and agitated depression.

* A curiously high incidence of disorders of the thyroid was encountered in addition to the usual cases of low basal metabolic rate. Four patients had had thyroidectomy performed several years prior to the onset of Addison's disease because of toxic goiter. Three additional patients were found to have adenomatous goiters without hyperthyroidism and 2, diffuse colloid goiters.

† This case is of interest because of the fact that hypertension persisted in spite of Addison's disease, even though the patient was not treated with desoxyeortico-sterone acetate. At necropsy, the adrenal glands were found to be atrophic.

Fortunately for the purpose of this study there were 19 patients* who refused to adhere to the low potassium diet after they left the hospital. These patients, however, did continue to take sodium chloride, sodium citrate and varying amounts of cortical extract. They, therefore, comprise a fairly satisfactory control group which one may compare with the group of patients who did adhere to the low potassium diet.

Table 1 shows the difference between the control group and the group treated with the low potassium diet. Among the latter, 88% lived more than 1 year and 40% lived more than 4 years after beginning treatment. Of the control group, only 53% lived more than 1 year, and only 18% were alive at the end of 4 years. The difference in survival is even more striking if it is calculated from the date of onset of symptoms; however, this method of calculation is open to the objection that the exact time of onset of symptoms usually cannot be determined.

TABLE 1—SURVIVAL RATES COMPARISON OF PATIENTS RECEIVING LOW POTASSIUM DIET WITH A CONTROL †

Period years	Low potassium diet			Control group		
	Patients traced ‡	Lived beyond indicated period		Patients traced ‡	Lived beyond indicated period	
		No	Per cent		No	Per cent
1	50	44	88	19	10	53
2	34	23	68	18	4	22
3	25	16	64	13	3	23
4	10	4	40	11	2	18

The mean length of life of those who died after the diagnosis had been made at the clinic was 2 years in the group which was treated with the low potassium diet; of those whose diet was not restricted, 1 year. Calculated from the onset of symptoms the mean duration of the disease among those who died in the former group was 3.6 years and in the latter, 2.2 years.

Of the 23 patients who died while being treated with the low potassium diet, 11 died in crisis. In the remaining 12 cases, death occurred because of an associated complication which in some instances probably would not have proved fatal if the patient had not also had Addison's disease. Among these complications were acute appendicitis, quinsy, unexplained fever and active tuberculosis. One patient died after flagrantly neglecting his diet.

* Eight additional patients were excluded from the control group because of severe complicating disease such as advanced tuberculosis

† The controls followed the same treatment as the patients on low potassium diets except for restriction of the intake of potassium. This treatment included an adequate supply of sodium chloride and sodium bicarbonate together with daily or periodic injections of adrenocortical extract

‡ Inquiry as of July 1, 1940. The 1-year group comprises patients seen at the Clinic whose condition was diagnosed as Addison's disease 1 or more years prior to the time of inquiry, that is, patients seen June 30, 1939, or earlier, the 2-year group comprises patients seen as of June 30, 1938, or earlier, and so forth

A woman, after adhering rigidly to her diet for several months, died dramatically within 6 hours after a dietary debauch. Two patients discontinued the diet and were treated with desoxycorticosterone acetate elsewhere. One of these was treated by the subcutaneous implantation of a very large amount of desoxycorticosterone acetate. At necropsy a few days later hydrothorax, ascites, hydropericardium and edema were present. In the other, hypertension occurred before death.

We know of 18 patients who are still being sustained by the low potassium diet, sodium chloride and sodium citrate. Only 3 of these patients require cortical extract regularly; the remainder use it during periods of stress such as respiratory infections and other intercurrent illnesses. Of these 18 patients, 8 are able to work at their regular occupations the entire year, 2 are able to work except during very hot weather, 7 are working part time, and 1 is unable to work at all.

Fourteen patients who had been maintained on the low potassium diet were treated subsequently with daily hypodermic injections of desoxycorticosterone acetate. At the same time the low potassium diet was discontinued. Following the change in treatment the health of these patients improved so that at present all but 2 of them are able to carry on normal activities.

Nine patients were treated with a *low potassium diet, high intake of sodium salts, and desoxycorticosterone acetate*. This method of therapy did not produce good results. Only 1 patient remained well. Two others contracted diarrhea and other symptoms which were interpreted by them as suggestive of impending crisis. These symptoms disappeared in 1 after discontinuance of the desoxycorticosterone acetate and in the other after discontinuance of the low potassium diet.

Five of the 6 other patients treated with desoxycorticosterone acetate while receiving a low potassium diet died within 2 months after beginning this type of treatment. Another died 6 months after treatment was instituted. All of these deaths, it is important to emphasize, occurred during the summer of 1939 when the danger of the concurrent use of a low potassium diet, a high sodium intake and desoxycorticosterone acetate was still unknown.

The terminal illnesses of these 6 patients are of considerable importance, as they illustrate not only the dangers of a high sodium, low potassium intake when used in conjunction with desoxycorticosterone acetate but also the dangers of this substance itself and its limitations as complete replacement therapy.

Case Reports. One of the patients, a woman aged 39, became edematous while taking a low potassium diet, 10 gm. of sodium chloride, 5 gm. of sodium citrate and 5 mg. of desoxycorticosterone acetate daily. With the onset of edema the intake of sodium chloride was reduced to 6 gm. daily and the low potassium diet was discontinued. Nevertheless the edema persisted and the

blood pressure increased to 160 mm. of mercury systolic and 110 diastolic. Pulmonary edema and dilatation of the heart followed. Death occurred suddenly.

The blood pressure of another patient, a man, rose to 160 mm. of mercury systolic and 100 diastolic while he was taking only 2.5 mg. of desoxycorticosterone acetate and 6 gm. of sodium chloride daily. General malaise and tightness of the chest were terminal complaints. Death occurred at home. There is no information regarding edema.

The third patient, a woman, died at home 2 months after the onset of treatment. She was taking 10 gm. of sodium chloride, 5 gm. of sodium citrate and 5 mg. of desoxycorticosterone acetate daily. Her attending physician reported that cyanosis, coma, convulsions and hypertension (160/?) were terminal symptoms.

The fourth patient, a woman, felt well for some time after implantation of 368 mg. of desoxycorticosterone acetate. She took in addition 6 gm. of sodium chloride. The diet contained only 3 gm. of potassium. After the onset of tonsillitis death occurred within 3 days. There was not any terminal edema or hypertension.

The fifth patient was an emaciated woman who had been getting along on a low potassium diet. She was admitted to the hospital because of nausea, weakness and symptoms of crisis. These symptoms may have been precipitated by the very hot, humid weather which prevailed at that time. Treatment consisted of intravenous injections of sodium chloride and sodium citrate, 40 to 80 cc. of cortical extract and 10 mg. of desoxycorticosterone acetate daily. Death occurred 3 days after the onset of treatment. Hyperpyrexia and hypotension were terminal symptoms. At necropsy the significant findings were bilateral adrenal atrophy, hydrothorax and cardiac dilatation.

The therapeutic program in the sixth case consisted of a low potassium diet, 5 gm. of sodium chloride, 2.5 gm. of sodium citrate and 5 mg. of desoxycorticosterone acetate daily. Six months after the onset of this regimen the patient, a woman, suddenly died during sleep. There were no premonitory symptoms.

It became apparent from these unfortunate experiences that either we were not using desoxycorticosterone acetate to the best advantage or that the substance itself constituted inadequate replacement therapy. The findings at necropsy in 2 cases suggested congestive heart failure as the cause of death. Both clinical and chemical evidence indicated that excessive sodium and water were being retained and it appeared probable that the low potassium diet and the high intake of sodium salts were partially responsible for this retention. This suggestion was further strengthened by the studies of Tooke, Power and Kepler.⁸ They showed that the patient who has Addison's disease has a normal response to salt deprivation and excess intake of potassium when treated with desoxycorticosterone acetate. This work indicated that the low potassium diet is at least superfluous if not dangerous.

The available evidence, therefore, suggested that the fault lay not with desoxycorticosterone acetate itself but with the manner in which it was being used. Treatment consequently was modified so that each patient who was given desoxycorticosterone acetate was also given a diet that contained an amount of potassium which was

equal to that in an average diet. The administration of sodium citrate was discontinued. Such a diet also permitted the intake of an adequate amount of protein and in addition eliminated the necessity of vitamin supplements.

Thirty-two patients having Addison's disease have been treated since these changes were made (Table 2). As has been mentioned previously, 14 of these patients had been treated with the low potassium, high sodium regimen. Thus far only one fatality has occurred. In this case the patient had a prolonged fever and a high sedimentation rate, possibly as the result of tuberculosis. Two of the patients who were getting along very poorly with desoxycorticosterone acetate and the low potassium, high sodium intake have been well since changing their diet. One of these patients has received implantations of pellets of desoxycorticosterone acetate on two occasions.

TABLE 2.—CONDITION OF PATIENTS TREATED WITH DESOXYCORTICOSTERONE ACETATE AND AN UNRESTRICTED DIET.*

	Patients.
Dead	1
Able to be up and about but unable to work	5
Able to work most of the time	10
Able to work full time	16
	<hr/>
Total	32

* It is impossible at this time to compare this group as to survival rate, for none of these patients has received desoxycorticosterone acetate therapy longer than 20 months.

Sixteen of the 31 patients that are now being treated with desoxycorticosterone acetate are able to work every day and state that they feel well, 10 are able to work most of the time, and 5 are able to work occasionally. All the patients are instructed to take from 2 to 5 gm. of table salt daily. The daily dose of desoxycorticosterone acetate varies from 2 to 5 mg. and is taken hypodermically. The preparation is dispensed in sesame oil. The patients are urged to eat liberally and are advised to eat before retiring because of the possible danger of hypoglycemia. If the patient is unable to eat and the daily intake of potassium therefore falls below 4 to 5 gm., supplementary potassium in the form of potassium chloride tablets may be taken.

We still believe that the treatment of choice for Addisonian crisis is the administration of large amounts of cortical extract and intravenous injections of solution of sodium chloride to which sodium citrate is added. This form of treatment has the great advantage of producing effects promptly. After the crisis has been treated successfully, the administration of desoxycorticosterone acetate can be instituted. During periods of infection, cortical extract may be used in conjunction with desoxycorticosterone acetate. Whether such supplementary treatment is either necessary or advisable is a matter which we have to determine. The assumption underlying such a supplementary use of cortical extract is based on experimental evi-

dence which indicates that the administration of desoxycorticosterone acetate does not constitute complete replacement therapy. The usual cortical extract is comparatively weak in its capacity to cause retention of sodium and water and therefore can be given with comparative safety. If for any reason (usually economic) the patient cannot be treated with desoxycorticosterone acetate, treatment with the low potassium diet and a high intake of sodium salts is of value and remains the cheapest form of therapy.

In conclusion, we wish to emphasize the fact that desoxycorticosterone acetate, like insulin, is a two-edged weapon. It is a highly potent compound with the capacity of doing irrevocable damage when used indiscriminately. This dangerous potentiality is further increased if either the intake of sodium salts is too high or the intake of potassium too low. Here again the analogy to the relationship between the intake of carbohydrate and the dosage of insulin is apropos. The appearance of edema, rising blood pressure to hypertensive levels and evidence of a mounting venous pressure are danger signals which should warn the clinician to reduce the dose of both sodium chloride and desoxycorticosterone acetate. Finally, it should be remembered that the patient, when first treated with desoxycorticosterone acetate, is in a physiologic state that is entirely different from what it will be several weeks later after the disease has been controlled adequately. At first there is a marked deficit of sodium chloride in the tissues. Later the store of sodium salts and water has been replenished and in these respects at least the patient is in a physiologic state that approaches normal. When this approach to normalcy occurs the dose of desoxycorticosterone acetate should be reduced. If it is not reduced, the combined effects of a mounting blood pressure, a rising blood volume, a rising venous pressure and a weakened myocardium may vitiate an otherwise brilliant therapeutic result.*

Summary. Good results have been obtained in the treatment of patients who have Addison's disease by the use of desoxycorticosterone acetate and an unrestricted diet. If the patient cannot be treated with desoxycorticosterone acetate, treatment with a low potassium diet and a high intake of sodium salts is of value. However, the two types of treatment should not be combined. The

* Large doses of desoxycorticosterone acetate can be given to normal persons for short periods. Studies of the chemical composition of the blood will demonstrate the fact that retention of sodium and excretion of potassium have occurred. The healthy myocardium will tolerate these changes with impunity for a longer period than will the damaged myocardium. On the other hand, the patient who has Addison's disease does not have a normal myocardium. Furthermore, there is some experimental evidence that desoxycorticosterone acetate has much less effect on restoring muscle efficiency than it has in storing of salt and water. Under such circumstances, therefore, it is not surprising that rapidly progressive congestive heart failure with sudden death should occur. Such sudden deaths have often been attributed to hypoglycemia, but the available evidence in our opinion favors the view that in this instance, as in most others, sudden death implies failure of the heart.

treatment of choice for Addisonian crisis is the administration of large amounts of cortical extract and intravenous injections of solution of sodium chloride and sodium citrate.

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BOOK REVIEWS AND NOTICES

BIRD MALARIA. By REDGINAL HEWITT, Sc.D., Department of Protozoology, School of Hygiene and Public Health, The Johns Hopkins University. (The American Journal of Hygiene Monographic Series, No. 15, July, 1940.) Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 228; 33 illustrations and 13 plates (1 in color). Baltimore: The Johns Hopkins Press, 1940. Price, \$1.10.

FEW groups of parasites have been so extensively studied as have the plasmodia of birds; and the greater part of this work has occurred during the last 15 years. Whether or not results justify the effort is not the concern of this review. The various species of parasites of the genus *Plasmodium* that occur in birds are easily and conveniently studied in canaries and other avian forms that are adaptable to laboratory work. Certainly much has been learned and much remains to be learned of malaria in man. These parasites of birds have been and should continue to be convenient research tools in attaining a more complete understanding of the disease as it affects man. And to have the scattered publications on this subject collected and their contents analyzed and interrelated should be immensely helpful. The chapter headings indicate the contents: I. The Discovery and Early History of Bird Malaria; II. Geographical Distribution, Incidence and Host Records; III. Experimental Hosts and Methods; IV. Species of Bird Malaria Parasites; V. Characteristics of Laboratory Infections; VI. Symptomatology and Pathology; VII. Immune Reactions; VIII. The Effects of Drugs and Chemicals on Infections; IX. The Sexual Cycle and Mosquito Transmission; X. Exo-erythrocytic Stages Associated with the Life Cycle; XI. Problems for Investigation.

On the whole, the treatment of the subject seems adequate, and, although it is poorly written and repetitious passages occur, workers in this field will be indebted to Dr. Hewitt for this work. H. R.

HANDBOOK OF ANÆSTHETICS (FORMERLY ROSS AND FAIRLIE). Revised by R. J. MINNITT, Trinity College, Cambridge, M.D. (LIVERPOOL), D.A. (R.C.P. and S. ENG.), Lecturer in Anæsthesia, University of Liverpool; Director of Anæsthetics, David Lewis Northern Hospital, Liverpool, etc. With Chapters on Local and Spinal Anæsthesia by W. QUARRY WOOD, M.D., CH.M., F.R.C.S.E., Surgeon, Edinburgh Royal Infirmary. Pp. 364; 102 illustrations. Fifth Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, \$4.00.

THE value of a handbook of anesthetics would appear questionable in this country where anesthesia is chiefly given by nurse anesthetists who would not understand the text, or by trained physicians for whom it is too elemental. This may be too handsome a compliment for the new speciality of Anesthesiology, but there is no doubt of the aim of those interested in furthering physician-anesthetists.

Minnitt expresses his hesitancy in rewriting the Handbook completely at first, preferring to wait for enough time to elapse since the passing of his predecessor to make the task less delicate. One hopes he will persevere with his intention to "build a more thorough account of recent research in future editions."

To American anesthetists the book will be of interest because of detailed descriptions of equipment for administration of inhalation agents. The chapters on local and spinal anesthesia are sketchy, and there is even less on intravenous anesthesia.

The principles of anesthesia as expressed in the little volume are sound and are obviously those of an individual with wide experience in nitrous oxide, ether and chloroform anesthesia. Its value on this side of the Atlantic lies, therefore, in presenting to this country some of the ideas of English anesthetists—a function not without merit especially on the technical side.

R. D.

THE PHARMACOLOGICAL BASIS OF THERAPEUTICS. A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students. By LOUIS GOODMAN, M.A., M.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine, and ALFRED GILMAN, Ph.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine. Pp. 1383; 126 figures and 67 tables. New York: The Macmillan Company, 1941. Price, \$12.50.

THIS is by far the most important book on Pharmacology and Therapeutics that has appeared in many years. It is not merely a "re-write" of other texts, but an entirely new book written in a style that should make it interesting to medical students and clinicians alike. It contains a number of appealing features: an excellent historical section prefacing each chapter, doses that are not merely tabulated but discussed in detail in relation to clinical conditions, a good chapter on prescription writing, and at last a really complete index.

While great stress is laid upon practical considerations of therapeutics, theoretical aspects are discussed better than in any other standard text. This applies particularly to the section on the autonomic nervous system and its relation to drug actions. Other features meriting special praise are the chapters on the chemotherapy of syphilis, on the sulfonamides (100 pages), on digitalis, and on anesthetics. While the criticism may be made that the book is too long for student use, yet this Reviewer feels that it is certainly the finest Pharmacology book in the English language.

J. C.

AMERICA ORGANIZES MEDICINE. By MICHAEL M. DAVIS, Chairman, Committee on Research in Medical Economics. Pp. 355. New York: Harper & Brothers, 1941. Price, \$3.00.

THERE is a widespread conviction in this country that medical science and medical practice are of great service to national life as a means of raising the level of health, happiness and efficiency, and that this service is at present not as available as it should be to all the people. Although the expectations of medicine are often exaggerated by the public, it is clear to everyone that methods should be devised for a better distribution of medical care without lowering its quality.

There are many problems involved in devising such methods that will be acceptable to both the medical profession and to the public. These problems have been given years of study by the author of "America Organizes Medicine." The results of his study are now fully presented in a book impressive for its thoroughness, soundness and well-balanced discussion.

The subject of the organization of medicine is treated in three parts: The first part, "The Changing Shape of Things," deals with various problems of medical practice emerging from social and economic changes caused largely by the rapid expansion of medical knowledge, the inevitable develop-

ment of medical specialism and the demands of the public for an extension of medical care.

The second part of the book is concerned with the problems that have been encountered in efforts to organize medical service and methods of paying for it. The third part, "The Emerging Shape of Things," discusses the pros and cons of a few principles that seem essential for progress in the organization of medical care, and certain well-considered recommendations for action in this field are made. Many questions are raised throughout the book for which answers must be sought by the medical profession, by the lay public or in many instances by professional and lay collaboration.

The chapter on Federal Policies and State Legislation is of particular value as throwing light on some of the less understood and most widely discussed phases of medical organization, which have been the subject of prolonged arguments under the titles, "State Medicine" or "Socialized Medicine."

This book is an important and valuable contribution by an outstanding student of medical sociology and should serve to give a better understanding of the problems of medical care, of which both the medical profession and the public are in need.

G. R.

DISEASES TRANSMITTED FROM ANIMALS TO MAN. By THOMAS G. HULL, PH.D., Director, The Scientific Exhibit, American Medical Association. Fourteen Contributors. Pp. 403; 43 illustrations. Second Edition. Springfield, Ill.: Charles C Thomas, 1941. Price, \$5.50.

For this second edition Dr. Hull has been fortunate in obtaining collaborators who are recognized authorities in their particular fields of veterinary medicine and bacteriology, parasitology, virus diseases and public health. The plan of this edition is identical with that of the first. Section I (Diseases of Domestic Animals and Birds) contains new chapters on Louping Ill, Sore Mouth in Sheep, Equine Encephalomyelitis, Rift Valley Fever, and Fungous Diseases. In Section II (Rodent Affections) chapters on Typhus Fever and Relapsing Fever have been added. Pertinent references are appended to each chapter. The text is brief, concise and informative. It should continue to hold an important place in the literature of public health and preventive medicine.

H. R.

A HISTORY OF MEDICINE. By ARTURO CASTIGLIONI, M.D., Formerly Professor at the University of Padua; Research Associate in the History of Medicine at Yale University. Translated from the Italian and Edited by E. B. KRUMBHAAR, M.D., PH.D., Honorary President of the American Association of the History of Medicine. Pp. 1053; 443 illustrations. New York: Alfred A. Knopf, Inc., 1941. Price, \$8.50.

THE Krumbhaar translation of Castiglioni's History of Medicine represents an effective combination of unusual value for the teaching of medical history. Castiglioni published the first edition in 1927 in Padua, a University with a long background of notable scientific achievement. Inevitably the history, written primarily for an Italian audience, emphasized Italy's important part in the development of medicine. Some of the most brilliant advances had been made by Italians or with opportunities made available by Italy, as in the case of Vesalius and Harvey. On the other hand, continuing great movements have seldom been the result of the effort of any single group. The question of priority in the development of parts of the whole becomes a matter of interpretation. Therefore, a comprehensive treatment by two able historians with quite different training and differing point of view is valuable.

The English edition based on the second Italian edition of 1936 is not a mere translation. Much has been added and minor items in the original, chiefly of local interest, have been omitted. The result is a more balanced work brought up to date. Even the few years intervening between the Italian and English editions, with rapid development in chemotherapy and other branches of medicine, have called for certain special additions.

Both authors were obviously concerned over proper balance in presenting the different periods of medical history, a difficult task with the necessity of preserving a full account of origins, on the one hand, and giving comparable recognition to the significant achievements of later years, on the other. Who did more for the advancement of medical understanding, Celsus or Osler, Paré or the Mayos? How difficult it is to give to each his just proportion! All modern histories of medicine appear to hurry in the final chapters, and this is no exception. Yet as much space is given to the last century and a half as to the 2000 years between Hippocrates and Vesalius. Krumbhaar has added hundreds of details to the already comprehensive treatment of recent advances given by Castiglioni. A simple illustration, one of many that might be cited, is the short but accurate account of investigation on the vitamins, two pages, concisely written, covering accepted knowledge.

Recent developments in medical education, organization of research and publication of new knowledge are excellently treated. The brief section entitled "The Study and Practice of Medicine" has unusual importance for the student of trends in medical history. The history of medicine is not simply a catalog of the past, but a living record, providing clear indications for building on past success and clear implications for avoiding previous mistakes.

The style of the translation is fluent and vigorous. The printing is excellent. The illustrations have lost something in reduction from the larger size in the Italian edition, but are still first class. The general and subject bibliographies—considerably enlarged in this English edition—and the appended chronological list of universities and medical schools will be useful to students, investigators and historians. The longer subject index is a distinct improvement. Altogether the book is an important addition to American medical and historical literature.

E. L.

THE PRINCIPLES AND PRACTICE OF OPHTHALMIC SURGERY. By EDMUND B. SPAETH, M.D., Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania, Philadelphia; Attending Surgeon, Wills Hospital, etc. Pp. 886; 451 engravings containing 1149 figures and 6 colored plates. Second Edition, revised. Philadelphia: Lea & Febiger, 1941. Price, \$10.00.

THE early appearance of the second volume of this textbook on ophthalmic surgery speaks for the splendid reception it has had. Very little new material has been added, but many of the unavoidable errors in the first edition have been corrected. It will continue to be a standard reference for ophthalmic surgery.

F. A.

DIETETICS FOR THE CLINICIAN. By MILTON ARLANDEN BRIDGES, M.D., F.A.C.P., Late Assistant Professor of Clinical Medicine and Lecturer in Therapeutics and Nutrition, New York Post-Graduate Medical School of Columbia University. Pp. 960. Fourth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$10.00.

FOUR editions in 8 years bear eloquent testimony to the favor with which this book has been received by the profession. The work of 23 contributors, it is distinguished by excellent balance and arrangement, easy availability for quick reference, and its practical point of view. It is highly recommended to every physician and student.

R. K.

THE DOCTOR AND THE DIFFICULT CHILD. By WILLIAM MOODIE, M.D., F.R.C.P., D.P.M., Medical Director, London Child Guidance, Clinic and Training Centre. Pp. 214. New York: The Commonwealth Fund, 1940. Price, \$1.50.

This little volume presents the fundamental principles and methods of child guidance for physician and medical student simply and clearly—also better than the vast majority of other books on the subject we have yet seen. The author, Medical Director of the London Child Guidance Clinic, is obviously a man of experience, sympathy and sound judgment. He makes no attempt to systematize the subject or group the well-known problems into strained categorical headings. Dr. Moodie opens with a "recognition of the problem," follows with a simplified but very useful chapter on the study of cases including histories and then proceeds with a section on evaluation of syndromes and general methods of treatment. There is then a more complete discussion of 18 specific behavior problems and psychoses.

The book is rather informal but that contributes to its value to the average physician. It is not a scientific treatise in the usual sense of the word, but is packed with timely, sound advice and common sense solutions to routine maladjustments. The Reviewer has been looking for a book like this to recommend to medical students and internes. E. T., Jr.

THE STORY OF CLINICAL PULMONARY TUBERCULOSIS. By LAWRASON BROWN, M.D., Late Director of Trudeau Sanatorium; Lecturer in Trudeau School of Tuberculosis. Pp. 411; 1 illustration. Baltimore: The Williams & Wilkins Company, 1941. Price, \$2.75.

THE lectures on the history of tuberculosis given by the author at the Trudeau School form the basis for this posthumous collection of essays. The development of ideas concerning the diagnosis and treatment of phthisis is shown in a series of "visits" with physicians in 1700, 1800 and 1900. Interest is centered chiefly on physical diagnosis, and the central figure of the book is Laennec. The spread of use of auscultation and percussion through Europe and the United States is traced in detail, and brief accounts are given of the development of roentgenologic diagnosis and of artificial pneumothorax and surgical collapse therapy. Physicians and surgeons especially interested in diseases of the chest as well as those interested in medical history will be delighted by this book, but everyone who uses the stethoscope, whether he be practitioner or student, will profit by acquaintance with this fascinating excursion into the relatively recent past. Readers of this journal will find particular interest in the final chapter, in which the author lists and discusses the articles on auscultation appearing in English and American medical periodicals before 1850. Foremost among these in the number of noteworthy contributions was the
H. I.

ESSENTIALS OF DERMATOLOGY. By NORMAN TOBIAS, M.D., Senior Instructor in Dermatology, St. Louis University; Assistant Dermatologist, Firmin Desloge and St. Mary's Hospitals; Visiting Dermatologist, St. Louis City Sanitarium and Isolation Hospital. Pp. 407; 143 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, \$4.75.

DR. TOBIAS has presented a valuable addition to the growing list of handbooks of dermatology for the student and general practitioner. In spite of the small size of the book, the author has in inimitable style condensed the essentials of dermatology without giving the reader the feeling

of reading a series of telegrams. In addition, the illustrations are well chosen and for the most part are well reproduced.

Although intention is expressed of discussing as far as practical each disease from the standpoint of internal medicine, the author does not stress the need for general physical examination in evaluating a dermatosis, for example. One other criticism is the inclusion of many rarities in a book on essentials. This is apparently done at the sacrifice of detail in some places, such as in the discussion of various diagnostic intradermal tests. It hardly seems advisable, moreover, to recommend for the general practitioner any arsenical antisyphilitic agent for a patient who has once suffered an arsenical dermatitis. (Cf. p. 82, where mapharsen is recommended after such an event.) On page 298, the histologic section (Fig. 90) labelled "senile keratosis" seems to the Reviewer to be good for seborrheic verruca (seborrheic keratosis).

Among the commendable features of this book are: specific statements regarding the general practitioner's limitations in handling various dermatoses—*e. g.*, gold compounds and Roentgen ray in lupus erythematosus; the modern viewpoint in the discussion of most conditions, especially eczema and dermatitis; excellent differential diagnostic tables; and the list of general therapeutic suggestions at the end of the book.

On the whole, the Reviewer unhesitatingly recommends this book for the student and the general practitioner who does not have the facilities nor the inclination to consult a larger volume.

H. B.

HERNIA. By ALFRED H. IASON, B.A., M.D., Consulting Surgeon, Long Beach Hospital; Director of Surgery, Brooklyn Hospital for the Aged; Surgeon, Manhattan General and Madison-Park Hospitals, etc. Pp. 1325; 355 illustrations by ALFRED FEINBERG, Instructor of Medical Illustration, Department of Pathology, College of Physicians and Surgeons, New York City. Philadelphia: The Blakiston Company, 1941. Price, \$15.00.

This large volume is presented in three sections: 1, Historical Evolution of Hernial Surgery; 2, Technical Aspects; 3, Medico-Legal Aspects. The introduction to this volume begins with a blistering attack on operators (which the author calls surgeons) and their practices "down to the mid-nineteenth century." He soon develops an evangelical fever in his method of presentation. The statements which he makes, while perhaps true, are dramatized to the extent of losing much of their effectiveness. Much of what is reviewed has nothing to do with herniæ. The descriptions of various older operative techniques are interesting and worthwhile from a historical viewpoint.

The statistical data are thoroughly presented, more so than is necessary, and the same can be said for many other sections of the book. No other volume on this subject presents the various subjects in so detailed a manner. It is in fact a work of reference rather than a monograph which surgeons will pick up and read from cover to cover.

Some of the discussions which are given under the section on treatment hardly belong in this volume. The suggestion that Lugol's solution be used to prepare thyrotoxic patients for operation for hernia demonstrates a lack of the relative importance of two surgical problems. Why status lymphaticus, diabetes mellitus, shock, and a large group of hepatic function and other tests should be described at length in this volume is not apparent. The paragraph on Hepatic Insufficiency on pages 444 and 445 is filled with inaccuracies. What possible use calcium chloride can have in hepatic insufficiency or acidosis, or even hemorrhage in jaundiced patients, is beyond the Reviewer's knowledge. Bleeding and coagulation times are not nearly

so useful as is the prothrombin time in determining the hemorrhagic tendency in jaundiced patients. Nor is there the slightest evidence that "It is this fat content—among other substances—which protects the tissues from injury due to volatile anesthetics." This section of the book could have been eliminated for it not only does not add to the usefulness of the volume but detracts from it because of gross inaccuracies.

The descriptions of the operations and the illustrations are good, but too many techniques are described. If this volume were rewritten and condensed to about one-third its present size it might be well received.

I. R.

RECENT ADVANCES IN ENDOCRINOLOGY. By A. T. CAMERON, M.A., D.Sc. (EDIN.), F.I.C., F.R.S.C., Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital. Pp. 432; 67 illustrations, including 3 plates. Fourth Edition. Philadelphia: The Blakiston Company, 1940. Price, \$5.00.

In spite of the title, this book is not limited to recent advances but gives an extensive survey of the present state of our knowledge in the field of endocrinology, dealing not only with recent reports but with fundamentals long ago established. Consequently, no special knowledge on the part of the reader is presupposed. The word "recent" is often applied to findings of 10 to 18 years ago, a period which is relatively old in this field. Probably this is accounted for by the wording of the first edition which has not been modified in this the fourth edition.

As the author is a biochemist, the discussion is more critical and authoritative when the chemical aspects of hormones are discussed. A lack of first-hand knowledge of morphologic changes is occasionally apparent. There seems to be an undue emphasis placed on British and Canadian sources, especially in regard to structural changes not generally accepted by pathologists. It seems to the Reviewer that this book could be improved by omitting mention of some reported findings that have not been substantiated and that no longer seem to be of interest even as possibilities.

On the whole, however, the book contains a fund of facts, systematically arranged, and clearly and simply stated, which serves a useful purpose in enabling practitioners and students to find readily available references to literature in a specialized field of science.

I. Z.

ORAL PATHOLOGY. A Histological, Roentgenological, and Clinical Study of the Diseases of the Teeth, Jaws, and Mouth. By KURT H. THOMA, D.M.D., Professor of Oral Surgery, and CHARLES A. BRACKETT Professor of Oral Pathology, Harvard University. Pp. 1306; 1370 illustrations, including 137 in color. St. Louis: The C. V. Mosby Company, 1941. Price, \$15.00.

THE author's well-known previous texts on dental pathology, diagnosis and treatment planning are climaxed by his *Oral Pathology*. This volume represents the most recent, extensive and detailed presentation of this subject. Those interested in referring to review articles or original source material will appreciate the extensive bibliographies included at the end of each chapter.

The chapters on dental caries, periodontal disease, the nutritional and endocrine aspects of normal and abnormal dental development afford a thorough review of the past work and current opinions in these fields. The author's experience and interest in the diseases and tumors of the jaws make these chapters the most interesting, authoritative and valuable of any in the book.

Patterned after his *Clinical Pathology of the Jaws*, the clinical, histo-

pathologic, roentgenologic findings and treatment are presented in detail. The numerous illustrations, which are one of the features of this text, contribute materially to a more complete understanding of the disease. The clinical appearance, the histologic and roentgenologic findings are illustrated for most of the diseases. Many of the photomicrographs and some of the clinical pictures are reproduced in color.

The common and uncommon diseases of the oral mucosa, lips and tongue are also discussed. The organization, completeness and authoritativeness of this section, for the most part, is not in keeping with the rest of the volume. No mention is made of the pathogenesis of some of the diseases, although the etiology is given; in others the pathogenesis is given in detail but no mention is made of the etiology. The colored figures (50 in number) illustrating this section are for the most part the best the Reviewer has seen. They comprise a valuable atlas covering this phase of oral pathology.

Adequate indexing of such an extensive work is a difficult task, yet a necessary feature in a reference text. More extensive cross-indexing would be desirable. It required several minutes to locate the text dealing with mixed tumors of the parotid gland. The Reviewer had occasion to look up syphilitic rhagades. This subject was not indexed. The indicated text on congenital syphilis made no reference to this condition or to Hutchinsonian teeth. The latter subject was indexed but no mention was made of the other symptoms of congenital syphilis. The text relating to this subject is found in four widely separated parts of the book, some without representation in the index. Keloids or Mikulicz's disease are not found in the index although a description of the latter disease is included in the text. These minor criticisms in no way lessen the reading value of the book, but do limit its usefulness as a reference source.

Thoma's *Oral Pathology* would be a valuable addition to any medical or dental library. It would be particularly useful to those interested in oral pathology or those interested in the clinical manifestation of oral pathosis. The publisher is to be complimented on the typography, the general excellence of the illustrations and the substantial binding.

L. B.

UNIVERSITY OF CALIFORNIA HOSPITAL FORMULARY AND COMPENDIUM OF USEFUL INFORMATION. Pp. 270. Berkeley, Calif.: University of California Press. 1941. Price, \$2.00.

In addition to the University of California Formulary with practical information on prescription writing, vehicles and many useful prescriptions, this work includes other valuable data such as emergency treatment and description of standard procedures in the medical, pediatric, dental, Roentgen ray and laboratory services. The book is well printed on thin paper, so that it is compact despite the wealth of material contained. It should prove to be a very convenient source of information to medical students, internes and practitioners.

J. C.

AN INTRODUCTION TO MEDICAL SCIENCE. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S. (CANADA), Professor of Pathology and Bacteriology in the University of Toronto, Toronto, etc. Pp. 358; 124 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$3.50.

AFTER 4 years, Dr. Boyd offers a second edition of this useful book. It is 42 pages longer and contains 16 more engravings, the changes being made "with the object of making the book of greater value to the nurse commencing the theoretical side of her training. There is a new historical chapter outlining the development of medicine from its early beginnings to its most recent triumphs. The chapter on bacteriology has been rewritten and

greatly amplified, including illustrations of all the common disease-producing bacteria. . . . New sections have been added on the clinical and laboratory methods used in the detection of disease, the uses of x-rays and radium, the vitamins, jaundice, pyelonephritis, purpura, agranulocytic angina, and the new wonder-working agents of chemotherapy." We repeat the views intimated in the review of the first edition of this book that it represents what an Introduction should be and is not to be confused with meretricious short-cut compends designed merely to help the parrot student "get by" his exams. We are glad to see retained in the considerably changed Preface of this edition the useful aphorism: "A little knowledge is a dangerous thing, but not if you know how little it is." E. K.

THE PHARMACOLOGY OF ANESTHETIC DRUGS. A Syllabus for Students and Clinicians. By JOHN ADRIANI, M.D., Instructor in Anesthesia, New York University College of Medicine; Assistant Visiting Anesthetist, Bellevue Hospital. Pp. 86; illustrated. Second Edition. Springfield, Ill.: Charles C Thomas, 1941. Price, \$3.50.

THIS small volume contains a great deal of information in outline form for those interested in the new field of Anesthesiology. Isolated facts in a variety of subjects are made readily available; the presentation is clear and there is a lengthy bibliography.

It is difficult to recommend this syllabus-type of work to one interested in reading for its own sake. The book can, however, be recommended to those preparing for examinations as well as to those organizing a teaching program. R. D.

START TODAY! YOUR GUIDE TO PHYSICAL FITNESS. By C. WARD CRAMPTON, M.D., Major, Medical Reserve Corps, United States Army; Formerly Director of the Department of Physical Education and Hygiene, New York Board of Education, etc. Pp. 224; illustrated. New York: A. S. Barnes & Co., 1941. Price, \$1.75.

WE agree entirely with the Preface to this book written by Alexis Carrel: "Today, more than at any other time of history, we need men who are physically and mentally fit. But physical fitness must not be separated from mental fitness. In his conception of physical fitness, Dr. Crampton includes not only the training of the muscles, but also that of the organs and of the mind. He aims at developing the whole individual, as well as his motor system, his glands, and his consciousness. Ultimately, man in the fullness of his virility. I am happy to recommend this most useful book to the men of America." E. K.

NEW BOOKS.

Elimination Diets and the Patient's Allergies. A Handbook of Allergy. By ALBERT H. ROWE, M.D., Lecturer in Medicine, University of California Medical School, San Francisco, Calif.; Consultant in Allergic Diseases, Alameda County Hospital, Oakland, Calif. Pp. 264. Philadelphia: Lea & Febiger, 1941. Price, \$3.00.

Play for Convalescent Children in Hospitals and at Home. By ANNE MARIE SMITH, Staff Instructor, Leaders' Training School, Community Recreation Service, Chicago, Ill. Pp. 133. New York: A. S. Barnes & Co., 1941. Price, \$1.60.

Start Today! Your Guide to Physical Fitness. By C. WARD CRAMPTON, M.D., Major, Medical Reserve Corps, United States Army; Formerly Director of the Department of Physical Education and Hygiene, New York Board of Education, etc. Pp. 224; illustrated. New York: A. S. Barnes & Co., 1941. Price, \$1.75. (Review above.)

- Life and Death at Low Temperatures.* (No. 1 of a series of monographs on general physiology, edited by B. J. LUYET.) By B. L. LUYET, Professor of Biology, and P. M. GEHENIO, Instructor in Biology, Saint Louis University. Pp. 341; 33 illustrations. Normandy, Mo.: Biodynamica, 1940. Price, \$4.50.
- Optical Activity and Living Matter.* (No. 2 of a series of monographs on general physiology, edited by B. J. LUYET.) By G. F. GAUSE, Professor of Experimental Biology, University of Moscow. Pp. 162; 18 illustrations. Normandy, Mo.: Biodynamica, 1941. Price, \$2.75.
- Orbital Tumors.* Results Following the Transcranial Operative Attack. By WALTER E. DANDY. Pp. 168; 100 illustrations. New York: Oskar Piest, 1941. Price, \$5.00.
- Berkeley Moynihan, Surgeon.* By DONALD BATEMAN. With a Preface by LORD MOYNIHAN. Pp. 354; illustrated. London: MacMillan & Co., Ltd., 1941. Price, \$4.00.
- Clinica del Trabajo.* Revista Mensual de Profilaxis y Seguridad, Vol. 1, March and April, 1941. Director General DR. OSCAR RODRIGUEZ REY; Forty-one Collaborators. Pp. 34. Buenos Aires, 1941.
- This new monthly review from the Argentine is a welcome addition to the journals on Hygiene and Social Medicine.
- The Precipitation of Clinical Symptoms.* Pp. 45 (Lithoprinted); 27 illustrations. (Reprint of Chaps. II and III of Vol. IV, Part 1 of "The Patient and the Weather," by W. F. PETERSEN and M. E. MILLIKEN.)
- Vascular Disease.* Pp. 129; 64 illustrations. (Reprint of Chap. V, of Vol. IV, Part 1.)
- Blood Dyscrasia.* Pp. 222; 112 illustrations. (Reprint of Chap. IV, of Vol. IV, Part 2.) Ann Arbor, Mich.: Edwards Brothers, Inc.
- These subjects are reprints from Volume IV of a series comprising 3205 pages and 1724 illustrations. The monograph is a masterpiece of research work that appeared during 1934, 1935, 1936 and 1937. As each of the four volumes was received it was given a careful review.

NEW EDITIONS.

- An Introduction to Medical Science.* By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S. (CANADA), Professor of Pathology and Bacteriology in the University of Toronto, Toronto, etc. Pp. 358; 124 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$3.50. (Review p. 279.)
- Accidental Injuries.* The Medico-Legal Aspects of Workmen's Compensation and Public Liability. By HENRY H. KESSLER, M.D., PH.D., F.A.C.S., Medical Director, New Jersey Rehabilitation Clinic; Formerly Medical Advisor, New Jersey Workmen's Compensation Bureau, etc. Pp. 803; 202 illustrations. Second Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, \$10.00.
- The American Illustrated Medical Dictionary.* A Complete Dictionary of the Terms Used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, Medical Biography, etc., with the Pronunciation, Derivation, and Definition. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., LIEUT.-COL., M.R.C., U. S. Army; Member of the Committee on Nomenclature and Classification of Diseases of the American Medical Association, etc., with the Collaboration of E. C. L. MILLER, M.D., Medical College of Virginia. Pp. 1647; 914 illustrations, including 269 portraits. Nineteenth Edition, revised and enlarged. Philadelphia: W. B. Saunders Company, 1941. Price, \$7.50.
- The 19th edition of this standard work includes more than 2000 new words, covering all departments of medicine and related sciences. Many of them are defined for the first time in the present edition of this book, undoubtedly the leader in its field.

PROGRESS OF MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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DISEASES OF COLON AND RECTUM.*

IN this review the subject of proctologic disease has been dealt with from a broad point of view. The discussion is confined to the local anorectocolonic disease without systemic involvement; to primary local disease with secondary involvement of distant regions, and to local disease as an expression of systemic disease.

Neoplastic Disease. Recently, all phases of polypoid disease of the rectum and colon have been extensively studied.^{5,25,26,33b,62,78,99,133} The term polyp as used by most writers refers to single or multiple pedunculated or sessile adenomas. Small islets of hyperplasia of the epithelium of the rectum and sigmoid are believed to be precursors of polyps. The great clinical significance of polypoid disease lies in its frequency of progression to malignancy. It is also believed that the polyps encountered in association with chronic ulcerative colitis may undergo adenomatous and malignant changes.²⁵ This is a clear-cut example of the transition from inflammatory hyperplasia of the mucosa of the bowel to the intermediary adenoma and finally to frank carcinoma.

The purpose of the treatment is the destruction of the polyps and the islets of epithelial hyperplasia by fulguration. This procedure is not without risk even in the hands of the expert operators. To prevent serious complications, such as perforation or hemorrhage, it is best to err on the side of conservatism¹²⁹ and to complete the fulguration in more than one sitting. Polyps occurring above the reflection of the peritoneum should be treated in a hospital; those present below the peritoneal reflection may be fulgurated in the office. Polyps of the colon situated beyond the safe reach of the sigmoidoscope are best removed by a transcolonic procedure.^{20,104}

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Multiple polyposis or adenomatosis is a heredofamilial, and perhaps a congenital, disease which nearly always undergoes malignant changes during the first three or four decades of life.^{89,91} Because of the widespread involvement of the colon, a colectomy in graded operations is indicated. In the absence of malignant changes of the rectum, the rectum may be saved in those instances where complete destruction of the polyps of the rectum and rectosigmoid by fulguration is possible. Following this procedure, an anastomosis of the ileum to the upper rectum or the lower sigmoid is made which is subsequently followed by a subtotal colectomy. Recurrent polyps of the rectum can easily be refulgurated.

As already inferred, adenocarcinoma of the rectum in many cases develops from previously benign polyps and may grow by extension on the mucosal surface and by invasion of the wall of the bowel.⁴¹ Then the spread occurs into the perirectal fat, and later upwards along the superior hemorrhoidal lymphatic pathway.^{26,55,56} When the lymphatics become blocked, retrograde and lateral spreads occur. The Miles type of combined abdominoperineal resection of the rectum with high ligation and division of the superior hemorrhoidal blood-vessels offers the best means for the radical removal of the rectal lesion and the involved perirectal tissues, mesentery and the high lying lymph glands.^{58,74,107,125} Whenever the neoplasm is near the level of the levator ani muscles, these structures should be excised widely because metastases occur along these muscles.⁵⁶ The perineal excision of the rectum with colostomy, such as described by Loekhart-Mummery, being a less formidable procedure than the abdominoperineal resection, is reserved for the extirpation of low rectal malignancies in patients who constitute poor surgical risks because of either advanced age or concomitant disease.

Surgical diathermy may be used for the treatment of advanced and inoperable cases of cancer of the rectum.¹³⁵ Surprisingly good results are observed in the occasional patient following this form of treatment. Fulguration has also been successfully employed for the treatment of early papillary adenocarcinoma of the rectum which is not fixed to the submucosa and the muscles of the rectal wall. In suitable cases, surgical diathermy may be combined advantageously with radium and followed by Roentgen irradiation.¹³⁴

For carcinoma of the colon, an ingenious and important procedure of temporary double-barrel colostomy with the purpose of isolating, defunctionalizing and debacterializing the colon distal to the colostomy has recently been described by Devine³⁷ and modified by Ochsner, DeBailey and Rothschild.¹¹³ In this defunctionalizing colostomy the two ostia are separated widely to prevent fecal contamination of the distal stoma and the isolated bowel. Following the successful resection of the tumor-bearing colon and the healing of the anastomosis, the continuity of the bowel is reestablished by the use of a specially designed colostomy clamp.

The details of the management and the complications of permanent colostomy have recently been described.^{40,125}

The present-day superior results following colonic and major rectal surgery are largely due to the various operative technical refinements, the frequent transfusions of blood, the restoration of the normal balance of fluid, electrolytes and protein, and the administration of vita-

mins and of other essential substances of which the body may be deficient or depleted. Sulfanilamide administered preoperatively and postoperatively (or deposited in the peritoneal cavity at the conclusion of the operation) has aided in reducing the incidence of postoperative peritonitis. Sulfanilamide apparently exerts a bactericidal effect on the *Strep. hemolyticus* which is frequently isolated from the retroperitoneal tissues, the wall of the bowel, or on the mucosal surface of the neoplasm,⁸³ and a bacteriostatic effect on other organisms causing peritonitis.⁹⁰ A more recent study of the effect of sulfanilamide, sulfapyridine and sulfathiazole on experimentally produced *E. coli* infections in mice showed that sulfathiazole was the most effective of the sulfonamides.⁸⁰ On the basis of the results of this study, it was suggested that sulfathiazole be employed for the treatment of *E. coli* infections in man as well as for prophylactic purposes following operations upon the colon.

Diarrheas. A recent important study^{79,117} showed that diarrhea may occur as a postoperative complication in severely ill patients who have been in shock as a result of an operative procedure. This diarrhea is often caused by multiple focal colonic ulcerations which arise on a vascular basis. They have been explained by the assumption of a vasospasm which occurs as a compensatory vasomotor response in shock and have been reproduced by the experimental production of vasospasm.

Bacillary Dysentery. The recognition of acute bacillary dysentery is relatively simple. It has however not yet been established how long the dysentery organisms may remain active in the host and what percentage of acute cases lapse into chronicity.^{138c} In chronic bacillary dysentery and in carriers, the recovery of the specific organisms, especially the Flexner bacillus, is difficult because of the intermittency of excretion of these organisms.⁴⁷ The administration of acidophilus milk is said to facilitate the recovery of the late lactose-fermenters of Duval-Sonne.¹²⁷ The very recently improved culture media, *c. g.*, bacto bile salts (Difco), are said to be as specific for dysentery organisms as bismuth media are for the typhoid bacillus.

It is known that healthy individuals who give no history of an antecedent bacillary dysentery infection or digestive disturbance may harbor *B. paradyenteriae*.¹⁵ Apparently factors other than the presence of dysentery organisms are essential for the production of clinical manifestations of bacillary dysentery infections. It is possible that a qualitative *E. coli* deficiency may be of etiologic importance in bacillary dysentery. Utilizing Nissle's studies of the antagonistic index between *E. coli* and *Eberthella typhi*, Maner³¹ found "that *Escherichia coli* isolated from dysentery stools are invariably deficient in antagonistic characters, in all cases the symptoms being associated with a qualitative *Escherichia coli* deficiency." Vitamin deficiencies may be another important factor responsible for the clinical manifestations of bacillary dysentery. It has been shown that a diet deficient in vitamin A¹⁴² and in certain components of vitamin B₂ complex produces manifestations of bacillary dysentery in monkeys that were known to be carriers of *B. paradyenteriae*, Flexner.⁷¹

The acute form of bacillary dysentery is self-limited, hence the efficacy of any therapy in this disease is difficult to evaluate. Pectin substances containing pectin and bananas have been used exten-

sively.^{85,114,146,152,153} Sulfanilamide and its derivatives have been employed with encouraging results in experimental animals and in a number of clinical cases of bacillary dysentery.⁷³ Recently, during a pharmacologic study of the various sulfanilamide derivatives, Marshall *et al.*⁹⁶ encountered several highly antibacterial compounds which are water-soluble and yet poorly absorbed from the gastro-intestinal tract, making it possible to produce a high concentration of the drug in the intestine and a low concentration in the blood and tissues. One of these compounds was designated as sulfanilylguanidine. The application of this new principle to bacterial chemotherapy appears to be ideal for the treatment of acute bacillary dysentery and other bacterial infections that are predominantly or entirely localized in the intestine.

Transfusions of blood from artificially immunized donors for the treatment of chronic bacillary dysentery has been suggested.^{138d} The practical results obtained and the theoretical basis of this method of therapy justify the continuation of immunotransfusion therapy. Auto-genous vaccines also have a definite place in the therapy of chronic bacillary dysentery.

Chronic Ulcerative Colitis. Little has been advanced to clear up the existing confusion regarding the etiologic agent. Howard^{67a} and Kessel⁷⁵ question the etiologic rôle of Bagen's diplostreptococcus in chronic ulcerative colitis. Many investigators believe that a number of cases of chronic ulcerative colitis are a form of chronic bacillary dysentery.^{138c} A belief is also current that chronic ulcerative colitis is due to a yet unidentified organism (virus?) or to allergy in a certain number of cases.

The evaluation of any form of therapy in this disease is difficult because of the natural tendency for remissions and exacerbations. The prime object of the present-day medical treatment of chronic ulcerative colitis is the restoration of the grave nutritional deficiencies by the administration of adequate doses of all vitamins^{6,92} and especially of vitamins B complex and C, liberal transfusions of blood and frequent feedings of bland, nutritious foods with an excess of protein. The rectal instillation of cod-liver oil is a useful adjuvant in the treatment of the subacute and chronic cases.^{9,131b} Although sulfanilamide and its derivatives have not yet been given a sufficiently extensive trial to permit definite conclusions, this form of chemotherapy already shows promise.^{14,27}

In extremely ill patients with acute exacerbations of chronic ulcerative colitis, remissions can frequently be produced by the administration of antitoxic *B. coli* horse serum (Winkelstein). This form of therapy is still in the investigative phase.

Ileostomy should be performed when adequate medical treatment is failing. The mortality from this operation is decreased if intraperitoneal exploration and manipulation of the colon is avoided at the time of ileostomy.⁵² After a lapse of time, when the patient's general health is restored, colectomy in graded operations may be performed.²¹ Unless severely involved by perirectal suppurations and fistulas and polypoid degeneration, it may be possible to preserve the rectum in anticipation of a future ileoproctostomy.⁵²

Polyposis, stricture, anal abscess and fistula, and anal fissure are the important proctologic complications of chronic ulcerative colitis. During the active phase of the colonic disease, all anorectal complications

should be treated palliatively except for abscesses which should be drained. Fistulectomy should be avoided because anal incontinence frequently follows this operation.¹³⁰

Amebic Dysentery. Amebic infection is pandemic in the temperate zone. The incidence of amebiasis in various parts of the United States exceeds 10% or is about 10 times greater than the incidence of active tuberculosis.²⁴ Amebic infestation is generally transmitted by infected food handlers.¹²⁴

A comprehensive study of infestation of the colon with *Endamrba histolytica* and other protozoa and parasites includes a proctosigmoidoscopic survey, a microscopic examination of the feces and the scrapings from the inflamed mucosa or the surface of the ulcers. The granulomatous masses in the rectum should be studied histologically as they may either simulate or accompany malignant disease.^{22,39} A roentgenogram of the colon with the aid of barium sulphate should never be omitted because it may demonstrate additional granulomas in other parts of the large intestine, especially in the cecum. The complement fixation test has not yet attained universal acceptance because of the non-inclusiveness of the results; it is still of adjunctive rather than of primary value.^{116a}

Recently good results have been reported following the employment of a combination of carbarsone administered by mouth and cliniofon administered intrarectally as small retention enemata.¹⁰⁰ Intracolonic heat supplied by means of colonic irrigation with 1 to 5000 copper sulphate solution at a temperature varying from 45° to 47° C. has also been recommended.³⁶ It should however be realized that the eradication of the parasite following anti-amebic therapy does not always relieve the digestive complaints in many patients. In the absence of amebæ, these abdominal symptoms can be controlled by sedatives and antispasmodics, although they may recur after non-specific therapy has been discontinued.^{67b,116b}

The intestinal lesions in amebiasis requiring surgical treatment are: appendicitis, perforation with resulting peritonitis, massive hemorrhage, amebic granulomas, cicatricial stenosis and pseudopolyposis. The extraintestinal lesions include abscess of the liver, pleuropulmonary amebiasis, cerebral abscess, cutaneous ulcerations and abscess, abscess of the spleen and urogenital involvement.¹¹²

Mucous Colitis. "Mucous colitis" is very probably merely an expression of or a somatic response to nervous tension, such as anxiety, resentment and guilt.¹⁴⁷ Since inflammation of the colon is absent in "mucous colitis," this term should be abandoned, especially in view of the fact that by long usage the genitive ending "itis" has come to connote inflammation.

The mucosal changes observed during an attack of "mucous colitis" can to a degree be reproduced either by the topical application of pilocarpine or physostigmine to the colonic mucosa or by the oral administration of various drugs of the choline group to normal individuals.¹⁴⁷ These drugs exert their effect through the action upon the parasympathetic fibers of the autonomic nervous system.

The etiologic rôle of allergy has been established in some cases of "mucous colitis." This phase of the problem has to date been insufficiently studied.

Diverticulosis and Diverticulitis. Diverticula are usually acquired. In many cases the diverticula are of congenital origin which develop only in the presence of factors that make for the production of an acquired diverticulum (Beer). Asymptomatic diverticula are frequently encountered during the routine Roentgen ray examination of the colon with the aid of barium sulphate or during incidental abdominal operations;⁶¹ the presence of diverticula is not suspected unless a pathologic process sets in.⁴² The onset and the early course of diverticulitis may resemble acute appendicitis. Diverticulitis responds well to medical treatment in over 90 % of the cases but requires prolonged medical supervision. The complications of diverticulitis consist of perforation with abscess, acute perforation with peritonitis, peritonitis without perforation, perforation high in the rectum with consequent ischiorectal or ischioanal suppurations, pericolitis with peridiverticulitis and thickening of the bowel wall eventuating in partial or complete obstruction of the bowel, enterocolic or vesicolic fistulas and cancer. These conditions invariably require surgical intervention.^{4,16b}

There is considerable uncertainty as to what extent diverticulitis is incidental or etiologically directly contributory to the rare occurrence of cancer in the diverticular pouches.

Tuberculosis. The presence of viable or virulent tubercle bacilli in the terminal bowel in many cases of pulmonary tuberculosis with positive sputa causes contamination of the anorectal tissues.^{97,98} Hence the finding of tubercle bacilli by culture or animal inoculation is not significant in the study of the anal lesions in these patients. In contrast, the cultures and animal inoculation are conclusive in the study of anorectal lesions of patients with pulmonary tuberculosis who have negative sputa. The presence of tuberculosis in the anorectal granulation tissue on histologic examination is therefore an essential criterion for the diagnosis of a tuberculous anal lesion in the cases of active pulmonary tuberculosis with a positive sputum.⁹⁷ On a single section this is only positive in about 50 % of the cases, but when run in serial section it is at least 75 % positive.⁹⁷ In many cases a diagnosis of anorectal tuberculosis can be made clinically by the characteristic appearance of the anal lesion.⁹⁴

Anal fistulas and preëxisting suppurations occur about 10 times as often among the tuberculous as among the non-tuberculous patients; these anal lesions are encountered more often in patients with advanced than with early pulmonary tuberculosis and are less prevalent in private than in ward practice.⁹⁴

The cure of the tuberculous anorectal lesion demands radical surgical extirpation and meticulous postoperative care. Healing after operations is protracted in the patient with pulmonary tuberculosis who has a positive sputum and is but slightly retarded in the patient with negative sputum. In either case healing is complete following adequate surgical treatment which is augmented by measures aiming to improve the general health of the patient.

Venereal Diseases. *Venereal Lymphogranuloma.* This is a systemic disease with localized manifestations in the inguinal region, genital tract and the anorectocolonic tube.^{11,53b} The intestinal lesions consist of proctitis, colitis, suppurations, fistulas *in ano*, rectovaginal fistulas and stricture. The rectal strictures may be tubular or diaphragmatic

in character. Strictures and other rectal complications occur more often in women as a result of the spread of the virus through the direct lymphatic communication from the cervix, the posterior vagina and the fornices to the lymph glands in the pelvis and thence to the pararectal glands, producing perirectal infection and fibrosis. Women with primary lesions on the vulva usually develop bubos because these genital structures are drained by the superficial lymphatics to the inguinal lymph glands. Inguinal adenitis or bubo is believed to act as a barrier to the spread of the virus to the pelvic and pararectal lymph glands. In men, the occurrence of bubos is very common and rectal involvement infrequent because most of the lymphatic drainage from the external genitalia is predominantly superficial to the inguinal lymph glands. In the absence of an antecedent bubo or inguinal adenitis, anorectal complications in men are the result of the direct spread of the virus from a lesion in the posterior urethra to the pararectal lymph glands, or from the inguinal nodes through the femoral and inguinal canals into the endopelvic fascia and glands. Primary infection and the resulting proctitis and stricture may be brought about by anal coitus or by the use of contaminated enema tips.

A positive intracutaneous Frei test usually establishes the diagnosis of venereal lymphogranuloma. However, the finding of the virus in the bowel discharges or tissues constitutes positive proof that the virus is the cause of the intestinal lesions.^{115b}

Sulfanilamide, sulfathiazole, or Frei antigen are effective therapeutic agents exerting profound beneficial systemic as well as local effects.^{83c, 95} Sulfanilamide and sulfathiazole, because of their universal availability, appear to be the drugs of choice. The beneficial systemic effects are evidenced by the disappearance of fever and leukocytosis, the rise of the hemoglobin values, the reversion of the hyperglobulinemia toward the normal level¹²³ and the restoration of a sense of well-being. Chemotherapy produces a diminution, if not the total disappearance, of the perirectal infiltration and the exudate; the raw surfaces heal, and the rectal fibrous strictures become more easily dilatable⁹⁵ although sulfanilamide and sulfathiazole have no direct influence upon scar tissue. Since the institution of chemotherapy, surgical treatment of the anorectocolonic manifestations of venereal lymphogranuloma has been largely limited to incision and drainage of localized perianal and perirectal suppurations, to the performance of an occasional temporary colostomy for acute obstruction and the digital or instrumental dilatation of the fibrous strictures.

To obtain the best results and the maximum of safety, especially during the intensive phase of treatment, chemotherapy should be instituted in a hospital.⁹⁵ These patients, like those with other venereal diseases, are notoriously unreliable and it is dangerous to entrust potent drugs to them without proper daily medical supervision. Early toxic symptoms may go unrecognized as they are unpredictable.

Recently, intrarectal diathermy combined with Frei antigen was proposed for the treatment of rectal stricture.¹⁰¹

Gonorrhea. In man, anal gonorrhea is usually acquired through pederasty. Except for cases of anal intercourse, contamination in girls and women is believed to take place during the act of defecation when a simultaneous expulsion of gonococci-laden discharge from the vagina

and a normal eversion of the anal mucous membrane occurs. Suitable biologic conditions for the acquisition and maintenance of gonorrheal infection are furnished by the transitional epithelium of the intermediate zone of the anal canal, the anal ducts and the crypts of Morgagni. The infection may spread to the deeper perianal and perirectal structures through the anal ducts which lead to racemose multiglandular structures located in the perianal tissues, and penetrate the sphincter muscles, especially the internal sphincter. It is known that gonococci may remain alive and virulent for years in the anal structures and that reinfection of the genital tract may occur from the anal focus.

Sulfanilamide, sulfapyridine or sulfathiazole administered orally is effective in the treatment of anal gonorrhea in the absence of localized suppurations or poorly draining sinuses.^{138b}

Chancroid. This lesion is encountered occasionally in the anorectum and is acquired by the direct inoculation of the streptobacillus of Ducrey through pederasty, or, in the case of women, through contact with the penis during sexual intercourse. The diagnosis can be made fairly readily by smear with the aid of the Unna-Pappenheim stain, and by the vaccine test which is a specific intracutaneous reaction comparable to the Frei test. Sulfanilamide or sulfathiazole are specific for this lesion.^{30,84}

Syphilis. In the infant, multiple superficial circumanal fissures or shallow ulcers are strongly suspicious of congenital syphilis. Infants may also have condylomata, teeming with spirochetes, on the circumanal area.

In the adult, a chancre may occur anywhere in the circumanal area but it is usually found in the posterior arc of the anal canal. Recently, a chancre occurring in the mucosa of the rectum was reported.⁶⁸ The chancre may be acquired through the practice of pederasty, and in the case of women, inoculation may also occur through contact with the penis during sexual intercourse. The diagnosis should be made by dark-field examination. A positive test is conclusive, but a negative one does not exclude syphilis. Secondary syphilitic lesions comparable to the mucous patches in the mouth apparently have not been observed in the rectum. Perianal representation of generalized maculopapular eruptions as well as multiple superficial circumanal fissures comparable to rhagades have been noted. A very characteristic finding is perianal condylomata lata which contain numerous spirochetes.

In late syphilis, gummata, ulcerations and stricture of the rectum have been encountered. The character of these lesions may be altered by secondary infection. Repeated studies and a therapeutic test may be required to establish a definite diagnosis. This especially applies to the diagnosis of syphilitic rectal stricture. The occurrence of tabetic crises of the anorectum is rare. Systemic pathognomonic signs of central nervous system syphilis are usually present in addition to local manifestations, such as relaxation of the anal sphincters, or saddle-shaped perianal anesthesia.

Accepted antisyphilitic treatment should be instituted immediately after the diagnosis is established. In the early cases of anal syphilis the continuous system of therapy is recommended although one may use massive dose arsenotherapy by the intravenous drip method, the so-called 5-day cure.⁶⁹ In late syphilis, routine continuous therapy is

preferable. Local treatment is directed to the secondary contamination and infection, if present.

Vincent's Infection. This disease is caused by the symbiosis of fusiform bacilli and Vincent's spirillæ. This lesion has been observed on the perineum or in the perianal region. Treatment consists of the topical application of a paste containing of from 5% to 10% of arsphenamine, neoarsphenamine^{131a} or maphiarsen.

Granuloma Inguinale. This lesion is believed to occur in the anal and perianal areas, although recently a rare but apparently proved case of granuloma inguinale of the rectosigmoid with constriction and ulceration has been reported.²⁹ This is regarded as a disease of the skin and subcutaneous tissues with late or no involvement of lymphatics and lymph glands and is probably caused by the so-called Donovan bodies. These are most frequently found in the tissues (or secretions) with the aid of Dieterle's silver stain. The material from the surfaces of ulcers may also be studied by smear stained by Wright's method.

Tartar emetic administered intravenously or fuadin injected intramuscularly are specific for this lesion.

Neurologic Investigation of the Colon. An interesting study of the reactions of the rectal muscle to distention with air was made by Rosenberg and Langworthy.¹²⁰ They found contractions of the rectal wall in normal persons in response to sudden stretch; these contractions vary in different patients and may vary in the same patient under different circumstances. In hemiplegia and paraplegia the rectal wall is more resistant to distention. In general, these responses were more pronounced in patients with bilateral injury of the corticospinal fibers. Apparently there occurs a release of tone in the smooth muscle of the rectum from the normal control by the cerebral motor cortex.

Another important study dealing with the neurogenic disturbances of the colon is that of White, Verlot and Ehrenthel.¹⁴⁸ They utilized the colonmetrogram which is the filling curve obtained by slowly distending the colon with warm water; these graphs closely resemble the cystometrograms. The reaction of the colon to filling determines the character of the muscular tone, the alteration in function of the upper or lower motor neuron and whether the effect of a lesion is upon either the sensory or the motor portion of the reflex arc. Colonmetry reflects the motor activity and the sensation of the colon as a whole; it does not indicate circumscribed "disturbances" of the rectum or other portions of the colon.

Lesions of the motor fibers in the brain or in the descending spinal tracts (spastic paralysis) produce a hypertonic response to filling, but lesions in the sacral segments of the cord, cauda equina, or pelvic plexuses (flaccid paralysis) show a hypotonic response (atonic bowel). Colonmetry is also of value in the study of neurologic disturbances of defecation.

Megacolon. There is as yet no unanimity of opinion as to the etiology of congenital megacolon.³⁵ At present, the preponderance of evidence points to an imbalance of stimuli to the colon from the autonomic sympathetic and parasympathetic nervous system⁸⁶ as an important cause of this lesion. There may exist either a hyperactivity of the sympathetic or hypoactivity of the parasympathetic nerves or a still undetermined combination of neural influences.

Therapeutic management has made rapid strides in recent years.⁸¹ Daily hot irrigations of normal saline⁵⁰ and the employment of parasympathetic drugs are in vogue now. Acetylbetamethylcholine bromide administered orally (in combination with mineral oil) is quite stable in the body and produces prolonged stimulation of the parasympathetic nerves causing increased peristalsis and relaxation of the anal sphincters.⁸⁶ The restoration of the normal balance of fluids and electrolytes and the administration of vitamins and of other essential substances of which the body may be deficient or depleted is extremely important.

Surgical treatment is indicated in cases that are not medically tractable as well as for the relief of complications. Sympathectomy or sympathetic ganglionectomy will abolish the inhibitory stimuli of the colon; colonic function will improve and regular evacuations result, but the size of the intestinal lumen does not necessarily decrease as shown by postoperative Roentgen ray studies with the aid of barium sulphate.¹³ Spinal anesthesia, by inhibiting the sympathetic stimuli to the colon, may cause evacuations of the colon during the duration of the anesthesia and infrequently for a variable interval of time thereafter.

Children below 3 or 4 years of age constitute poor operative risks and, incidentally, in them the therapeutic benefits are minimal.³⁵ Patients with thin, weak colons as a rule respond poorly to any type of sympathectomy; in these cases ileoproctostomy followed by graded colectomy is indicated. Segmental colonic resections are useless because progressive dilatation proximal to the point of resection occurs too frequently.

The Rôle of the Colon in Urogenital Disease. There exists a close relationship between the intestinal and urinary systems. Pathologic activity of the colon, especially of the anorectum, under certain circumstances may initiate and perpetuate disease in the urogenital tract. The colon in the presence of pathologic activity or deranged function may act as a portal of entry for enteric organisms into the blood and lymph streams; in rare cases a diseased colon may act as a serious focus of infection.^{138a}

Apparently the lymphatics constitute an important route for the dissemination of infection from the anorectocolonic foci. There exists a communication between the lymphatics of the anorectum and the urinary bladder¹²¹ as well as between the anorectum and the upper urinary tract.¹²⁶ Long ago the existence of a direct lymphatic communication between the right colon and the right kidney was described; it is believed that a similar lymphatic route may exist on the left side.

Uroinfection caused by *B. paradyenteriae* and allied species have been described. It is believed that uroinfection caused by these enteric organisms may either follow or accompany bacillary dysentery, or occur in patients who present neither a history nor clinical evidence of intestinal bacillary dysentery. Apparently *B. paradyenteriae* and the allied species causing uroinfection originate in the colon notwithstanding the fact that bacillary dysentery has been regarded as a localized intestinal disease.^{38,111a,b}

Uroinfection caused by the organisms of the colon bacillus group occurs frequently in patients who have associated colonic disease or dysfunction. In such patients, Peretz and his associates, by studying

the different antagonistic colon bacillus indexes, found a definite qualitative relationship between the colon bacilli recovered from the urine and the feces. It was concluded that there exists a definite relationship between infection in the urinary tract and the pathologic states in the colon as well as between the types of colon bacillus present in the urinary tract and the colon. Recent studies have shown that in some cases stasis of fecal current and inflammatory and infectious diseases of the anorectocolonic tube are capable of producing and perpetuating moderate and subacute recurrent types of uroinfection which disappeared following the eradication of the intestinal foci.^{138a}

The "urologist's ulcer"⁶⁵ occurs in men who have received or are receiving massage of the prostate. This ulcer occurs on the mucous membrane of the rectum just above and over the prostate and seminal vesicles; it appears as a raw streaked almost fissured lesion and may undergo malignant degeneration.

Urogenital Complications of Malignant Disease of the Rectum. Following resection of the rectum, retention of the urine may occur which eventuates in pyelonephritis in many cases. In men, prostatitis and obstruction at the vesical neck may develop necessitating surgical intervention.⁶³ In women, contracture of the neck of the bladder is infrequently encountered. Because of lack of normal posterior support, the bladder sags causing an angulation with the urethra that gives a cystoscopic appearance of a moderately advanced cystocele. The bladder distends and becomes trabeculated and cellular; even small diverticula may form. The vesical changes and disturbances are to a large extent also due to direct operative trauma to the bladder and its parasympathetic fibers. The injury may be unilateral, incomplete, transitory, and, occasionally, permanent. The degree of the injury to the nerve supply of the bladder is dependent upon the extent of the malignant involvement and the fixity to adjacent structures.^{64,77} The duration of the urinary disturbances depends upon the extent and character of the nerve injury.

Anesthesia. The development of several reliable slowly absorbing oil-soluble anesthetic solutions constitutes a significant advance. However, the promiscuous and unintelligent use of these agents constitutes a retreat especially when employed in disregard of the cardinal principles of anorectal surgery.

The long-acting anesthetic solutions have been employed chiefly in the treatment of certain cases of pruritus ani and in selected cases of anal superficial fissures, as well as for the avoidance of postoperative pain and discomfort following hemorrhoidectomy. When used for the avoidance of postoperative pain, the injections must be made under aseptic precautions before the operation is begun. Gorsch advised that the injection of these anesthetic agents be made 24 to 48 hours before operation. There are however numerous competent proctologists who believe that when clean-cut and gentle surgery and meticulous pre-operative and postoperative care are employed, there is no need for the long-acting anesthetics (either oily or aqueous solutions); at best these agents are poor substitutes for good surgery.¹⁰⁵

The slowly absorbing anesthetic solutions are not devoid of hazards and pitfalls. The oil-soluble anesthetic agents may produce an aseptic inflammatory reaction of the tissues into which they are injected eventu-

ating in suppuration and necrosis. The long-acting water-soluble anesthetics, *e. g.*, eucupin-procaine solution, frequently produce edema, hyperemia, and bleeding; "their disadvantages seem to outweigh their advantages."⁴⁴ Idiosyncrasy to these drugs is also encountered at times.

The choice of anesthesia for anorectal surgery is of importance. The ideal anesthetic is one that will produce the best relaxation of the muscles of the anal canal and of the perineum. Spinal anesthesia using 5 to 7 mg. of pontocaine in 1 or 2 cc. of spinal fluid or 25 to 50 mg. of procaine hydrochloride crystals dissolved in 1 cc. of spinal fluid which is injected between the third and fourth lumbar vertebræ are the anesthetics of choice, especially when infection in the anorectal tissues is present.¹⁵¹ The incidence of postspinal headaches has been reduced, if not eliminated, by employing small lumbar puncture needles (22- to 25-gauge) and by keeping the patient in a horizontal position for from 8 to 24 hours after operation. Caudal and paravertebral block is a safe and effective but a difficult and time-consuming procedure even in the hands of the expert anesthetist. The average surgeon prefers low spinal anesthesia to caudal and sacral block because of the simplicity of execution and the promptness of the onset of anesthesia. Infiltration anesthesia using procaine hydrochloride enjoys the widest popularity because it lends itself to office practice. Infiltration anesthesia must never be employed in the presence of infection or in cases of questionable diagnosis. The distortion of the tissues caused by the injection of the anesthetic solution is a distinct disadvantage.⁷⁰ Inhalation anesthesia, usually cyclopropane, is employed only when the patient is apprehensive or refuses other types of anesthesia. Deep anesthesia is usually required because the muscles of the anal sphincter are the last to relax.¹⁵¹ Intravenous anesthesia is infrequently employed for short proctologic procedures, such as incision and drainage of superficial perianal abscesses, the removal of fecal impactions, or gauze packings from deep perineal wounds.^{70,151}

Pruritus. Intractable pruritus ani remains a problem difficult of solution because of the multiplicity of etiologic factors involved.

Physiologic Considerations. The circumanal region in common with the hairy parts of the axilla, labia majora, mons veneris and the areola of the nipple shares a wide distribution of the apocrine sweat glands.¹⁴⁵ These glands develop from the differentiated epithelium and begin to function at puberty. In women the apocrine glands are said to be hyperactive during pregnancy and the premenstrual period, and hypoactive during the intermenstrual phase and after menopause. This obvious relation of physiologic gonadal activity to the function of the apocrine sweat glands suggests that this sweat apparatus is related to, and perhaps is an integral part of the genital tract. The apocrine sweat glands also respond to neural and psychic stimuli.

The secretions of the apocrine glands contain an excess of carbohydrates and proteins and a pH ranging from 6 to 7 in contradistinction to the pH of from 4 to 5.5 of the ordinary sweat secreted by the eccrine sweat glands. The alkaline reaction plus the excess of carbohydrates and proteins of the apocrine secretions are the necessary ingredients for an excellent culture medium for certain bacteria and various fungi.

Other important physiologic considerations concern the disturbances

of fat secretion of the skin,¹³² the state of gastric secretion and the pH of the feces.¹

General Disease. The etiologic rôle played by general disease is minimized by some investigators and denied by others. Pruritus ani is occasionally encountered in diabetes mellitus and in pellagra. The rôle of allergy is little understood but frequently incriminated. Although patients with localized pruritus may have an allergic background there is no clear-cut proof that atopy is a necessary prerequisite for its development. However, sensitivity to foods and drugs is important in some cases.

Regional disease in the genital and lower urinary tracts may cause and perpetuate pruritus ani. Disturbances of the intestinal tract resulting in the alteration of the character and pH of the feces, or the presence of intestinal parasites may initiate pruritus ani.

Psychic Disturbances. The psychic factors are difficult to evaluate. One of the major problems is to determine what is cause and what is effect. Undoubtedly, localized pruritus can and often does cause nervous symptoms and also may be the last straw in upsetting a delicately adjusted mental equilibrium. From this standpoint localized pruritus is causative. Sulzberger, in agreement with others, asserted that severe pruritus may lead to a "complete disintegration of the morale and occasionally to suicide." On the other hand, pruritus ani undoubtedly can be a local organic manifestation having the same significance as any organ neurosis or hysterical symptom. In this case, the psychogenic factors are primary. In addition to these two thoroughly clear-cut situations we meet with a problem of a pruritus initiated by a local organic factor and the symptoms are utilized in the interest of a psychologic need. The perpetuation of the pruritus then serves as a most important psychodynamic function. This function may represent a substitutive gratification, a displacement to a new erotic zone, or a regression to an archaic erotic zone. Many of the patients in whom one suspects psychic factors fall into the group of obsessional neuroses.¹⁰²

Anal Lesions. Accumulating experience shows that the inflammatory and infectious anal lesions as well as pruritus ani in many cases have a common cause in infection of the preformed anal ducts, anal glands and the crypts of Morgagni. A cure cannot be expected unless both the infection of the anal structures and the anal lesions secondary to this infection are removed surgically. In the recurrent cases of pruritus ani following proctologic operation, it is possible that either the local anal lesions or the common underlying cause or both were incompletely eradicated.

Anal Hygiene. Poor anal hygiene brought about by fecal staining of the circumanal area is of major importance in the simple cases of anal pruritus; however, anal hygiene *per se* appears to play a minor rôle in the refractory or intractable cases.

Dermatologic Lesions. General dermatologic lesions having local anal representation are important causative factors in pruritus ani. Local dermatitis may be produced by the passage of feces containing an excess of skatole or other hydrocarbons¹³⁷ or by the therapeutic application of various drugs. The part played by perianal and anal dermatophytid has also received considerations.^{12,43}

Treatment. The treatment to be successful must be rational and based on sound physiopathologic principles. Because of the multiplicity of factors involved, the intractable or obstinate case presents almost insurmountable difficulties to all forms of therapy.

Rigid cleanliness is very essential. Lilienthal's method of applying bland ointments to the perianal region prior to defecation prevents fecal soiling and is effective in many cases.⁸⁷ Soap and other alkali should be interdicted especially in cases where there exists a deficiency of cutaneous fat secretion.¹³² Toilet paper containing injurious chemical substances and dyes should be avoided; cotton and olive oil should take the place of toilet paper and soap.

The local application of antiseptic, fungicidal and antipruritic drugs, especially resorcin, cocaine derivatives and mercury, may cause a dermatitis which aggravates the itching.¹³² Utmost caution should therefore be exercised when these drugs are employed.

The diet must be bland. If the feces are alkaline in reaction, an acid ash diet should be given, including large quantities of buttermilk¹ or acidophilus milk. In the presence of gastric hypoacidity or anacidity, hydrochloric acid or glutamic acid hydrochloride should be prescribed. The intake of carbohydrates must be reduced to prevent skin hydration which also favors pyogenic and fungous infections.¹³² Alcoholic beverages and highly seasoned foods must be absolutely interdicted.

Where food sensitivity is suspected, exclusion diets should be instituted. The intake of drugs, especially phenolphthalein and its derivatives, should be discouraged because of possible sensitivity.

Specific desensitization for perianal moniliasis⁴⁹ and dermatophytosis with autogenous or stock vaccine and fungous extract is still in the experimental stage and should be employed with caution because of the occasional alarming reactions.

Radiation therapy may be effective in reducing the hyperactivity of the sweat glands.¹³² Perianal hyperhidrosis in certain cases can be controlled by the application of a 4% aqueous solution of formalin.¹¹⁰

Of the numerous drugs that have been recommended for the topical application, gentian violet dissolved in water or alcohol, and Castellani's carbolfuchsin solution appear to be the most effective. The injection of oil-soluble long-acting anesthetics into the perianal tissues has afforded a permanent cure in a few and temporary relief in many cases.

Concomitant anorectal lesions, regardless of their etiologic importance in pruritus, should be eliminated in all cases of pruritus ani. When pruritus ani persists despite the foregoing therapeutic measures, radical treatment consisting in the perianal subcutaneous injection of alcohol^{16a} or the tattooing of the anal canal and the circumanal area with mercury sulphide^{66,138c,140} are required. The injection of alcohol is an established form of therapy and is effective in a large number of obstinate cases. To date, the results from tattooing have been most encouraging except in some cases with dry scaly perianal skin or in patients who had had excessive Roentgen irradiation of the perianal skin. Tattooing with mercury sulphide apparently produces a functional impairment of the cutaneous sensory terminals with a resultant alteration in the capacity of this neural system to respond to adequate stimuli. A change in the cutaneous modalities is produced which,

within limits, is proportional to the amount of intracutaneous deposit of mercury sulphide. This form of therapy is still in the investigative phase.

In the occasional patient with long-standing refractory pruritus ani, after a careful investigation of the psychic factors discussed previously, the guarded use of psychotherapy is of paramount importance. Without entering into the technical details of psychotherapy (which involve considerable difficulties) a warning note should be included: It must never be forgotten that a certain amount of pruritus may be an essential component of the mental equilibrium of the patient considered as a whole. As a corollary of this, a ruthlessly violent removal of so necessary and unconscious gratification can be followed by the most distressing sequelæ, even including self-destroying impulses.

From the foregoing it is apparent that there is no royal road to an easy appraisal and treatment of pruritus ani.

Hemorrhoids. The etiology, the comparative value of injectional and surgical therapy and the advisability of immediate or delayed operation for strangulated thrombosed internal hemorrhoids are still matters of controversy.

Infection in the perianal tissues, preceded or accompanied by passive congestion, appears to have gained serious consideration as an important factor in the etiology of piles in many cases. Infection of the crypts of Morgagni, anal ducts and multiglandular structures singly or together may produce perivascular inflammation which is apparently responsible for the formation of hemorrhoids. Campbell's¹⁹ clinical experiment is of interest: he removed the hemorrhoidal varices and purposely left the crypts of Morgagni undisturbed to see if chronic infection which persisted might lead to a recurrence of the piles. In the course of his study he became so convinced of the importance and seriousness of the crypts and the anal ducts that he lost courage to further pursue this study, and began to remove these anal structures routinely during hemorrhoidectomy.

The operation of choice is a non-traumatizing procedure that will eliminate the varices as well as the sources and channels of infection and provide ample drainage through open wounds in order to promote the restitution of the inflamed and infected anal and perianal tissues. The principles of such operation consist of: 1, excision of the crypts of Morgagni and the anal duct-bearing tissues; 2, extension of the wounds originating in the rectum or anal canal into the perianal tissues in order to provide adequate drainage; and 3, keeping the wounds open. The incisions are made in the long axis to the rectum and anal tube and are carried to the perianal skin in a radial manner.

Many surgeons treat irreducible strangulated internal piles (especially when spasm of the anal sphincters is present) by immediate operation;^{119b} some surgeons employ palliative measures and defer operation.^{51, 119a} The Reviewer combines early surgical treatment with the administration of sulfanilamide or sulfathiazole. Chemotherapy is given as an additional safeguard against the remote possibility of occurrence of pyelophlebitis or abscess of the liver.

Injectional therapy is the method of choice for moderate sized uncomplicated, soft, bleeding, prolapsing but spontaneously reducible internal piles. Exceptions are made if systemic disease or advanced age pre-

cludes operative interference.⁹³ Hemorrhoids associated with mild obstructive lesions at the vesical neck may be treated by injection of sclerosing solutions with good chances of success. Good results are also obtained in the treatment of internal hemorrhoids during the early months of pregnancy.

The contraindications to injectational therapy include mixed piles, evidence of recent or old inflammation or infection, neoplastic disease in the anorectocolonic tube or other concomitant local lesions requiring surgical treatment.

The main purpose of injectational therapy is to stop bleeding and to correct the associated prolapse. Following the injection of sclerosing solutions (quinine and urea hydrochloride 5% to 10% solution or 5% solution of phenol in pure almond oil are most popular) submucously or into the hemorrhoidal mass, a sterile inflammatory process is produced within the interstitial tissues of the hemorrhoidal plexus causing a chemical thrombosis of the vessels followed by sclerosis and fibrosis.

The techniques of injection vary with the experience of the operators. The solutions may be injected submucously or into the hemorrhoidal mass. A submucous injection above the anorectal ring about the pedicle of the hemorrhoid will obliterate the superior hemorrhoidal vein and fix the mucous membrane at high level to prevent prolapse.⁸⁸ Similar injections of the remaining piles are made usually at weekly intervals until all hemorrhoids have been injected at this high level. Subsequently weekly injections are made into the hemorrhoidal mass at a lower level. Occasionally additional injections have to be made submucously between the treated piles in order to correct mild descent. Personal experience with this method of injection performed during the past 18 months has been very gratifying.

Properly performed injections should not result in complications. Superficial sloughs are not of serious import, and occur as a result of superficial injection or as a result of the injection of too much solution.⁹³ Complications such as pain, bleeding, extensive ulcers, irreducible prolapse, strictures, abscess formation with subsequent fistulas, pyelphlebitis and septicemia have been reported. It is recognized that this method of treatment is neither simple nor without danger; it has definite limitations which should be understood lest disappointments and complications will result.

Injectational therapy apparently does not produce a permanent cure. Recurrences are dependent on the fate of the fibrosis produced and the elimination of the etiologic factors which had existed prior to the institution of this method of treatment. Since injectational therapy does not remove the original etiologic factors responsible for the development of piles, recurrence can hardly be considered a failure in those instances in which the underlying cause has not been eliminated.

Anal Fissures (Ulcers). *Acute Fissure.* Superficial, single or multiple fissures in the anal canal or circumanal area are usually produced either by trauma or irritation. These fissures show no adjacent inflammation or induration. They either heal spontaneously or with the aid of the topical application of bland ointments. Occasionally the long-acting oil-soluble anesthetic solutions are used to allay pain.

Chronic Fissure. This lesion consists of an ulcer with adjacent induration and inflammation¹⁴⁴ and dysfunction with fibrosis of the subcu-

taneous portion of the external anal sphincter muscle. The underlying cause of the chronic fissure (ulcer) resides in infection of the preformed anal ducts and crypts of Morgagni.^{16a} The frequent occurrence of this lesion in the posterior arc of the anal canal is due to the preponderance of crypts of Morgagni in the posterior portion of the anal canal.¹⁰⁸

An attempt has also been made to explain the pathogenesis of the anal ulcers on the basis of the anatomic arrangement of the various components of the external sphincter muscle. The superficial portion of the external anal sphincter muscle has a Y-shaped origin and insertion and lies above and external to the subcutaneous component of the external anal sphincter which is an unsupported circular muscle surrounding the anal orifice. Thus the subcutaneous portion of the external anal sphincter lies like a "bar across the crook of the Y" and is therefore subject to frequent trauma.^{10a}

Chronic anal fissures (ulcers) are best treated by wide excision of the ulcer-bearing area, including the involved crypt or crypts (and the sentinel pile, if present) followed by the division of the subcutaneous portion of the external anal sphincter muscle. The long-acting water- or oil-soluble anesthetics have no place in the therapy of this lesion because they are ineffective and dangerous. The operative treatment, because of the smooth convalescence and the inevitable successful issue is definitely preferable to taking even the slightest risk with the slow absorbing anesthetic agents.¹⁴⁴

The Pecten Band. Pectenosis has been regarded as a pathologic entity which is characterized by a circular constriction caused by a deposit of fibrous tissue in the submucosa at the pectinate line, and is said to be produced by chronic passive congestion. Its counterpart is sometimes found in globus hystericus when fibrous tissue in the submucosa forms opposite the cricopharyngeus muscle. A recent important study⁴⁵ showed that the submucosa in the region of the pectinate line contains involuntary muscle fibers continuous with the muscularis mucosæ of the rectum, which, in some cases, form a well-developed submucosal muscle close to but always distinct from the internal anal sphincter muscle. The term "muscularis submucosæ ani" was proposed for this submucosal layer of muscles. The rôle played by this muscle is not that of a fibrous band, as hitherto believed, but that of a muscle band exerting its effect through either spasmodic contraction produced by local irritation or hypertrophy resulting from chronic spasm and leading to stenosis.

Apparently this submucosal muscle had hitherto been overlooked by histologists. This is the explanation given by C. N. Morgan for the absence of reference to this muscle in his otherwise authoritative description of the anatomy of the anal canal.¹⁰⁸

Anal Abscess and Anal Fistula. The now well-recognized concept that these lesions originate from an infection in the preformed anal ducts^{16a} is worthy of reëmphasis. The anal ducts empty in the crypts of Morgagni but may lead to racemose multiglandular structures situated in the perianal tissues and may pierce the anal sphincter muscles, especially the internal sphincter. The anal ducts are lined with a secreting columnar epithelium which in branches is cuboidal, and may become natural incubators for bacteria under suitable conditions. Infection of these anal structures may lead to the development of peri-

anal and perirectal suppurations eventuating in anal fistulas. The primary openings of true anal fistulas are always found within a crypt of Morgagni.

Perianal fistulas occurring as a complication of regional ileitis have been reported.¹¹⁸ The accompanying infectious diarrhea is believed to produce infection in the crypts of Morgagni which in turn results in anal fistulas in most of these cases; in some instances, however, there occurs direct fistulization from the ileum to the rectum or perirectal tissues, which may become infected anywhere along its tortuous course.

Anal and perianal abscesses should be incised widely and drained adequately as early as possible. The T-shaped or crucial incisions with the removal of the skin and the infected deeper tissues between the crossed incisions (thus unroofing the abscess cavity) are most often employed. The abscess cavity is explored digitally and multilocular cavities, if present, are broken up and packed lightly with either iodoform or plain gauze. Fistulectomy combined with incision and drainage of the abscess may be performed in selected cases.

The fundamental principles of fistulectomy consist of the clean-cut excision of the fistulous channel with the adjacent infected tissues; the elimination of overhanging skin edges to promote adequate drainage, and the employment of light gauze packing for about 48 hours. Of equal importance is the correct and meticulous postoperative care.^{10b, 16a, c}

Extensive fistulas may require two-stage operations. At the first procedure, the fistulous tract or tracts are excised down to the sphincter muscles. The remaining portion of the channel is threaded with a seton and tied loosely. At the second operation, which is performed after a firm scar had formed in the lateral wound, the sphincter muscle is divided and the remaining portion of the fistulous tract is laid open.^{10b} This procedure prevents the wide retraction of the cut sphincter muscle with resultant anal incontinence.

Anal Incontinence. In general, this complication follows either obstetric procedures or operations upon the anal canal; it occurs most often following fistulectomy. In most cases, if not in all, anal incontinence is a product of unforgivable incompetence.^{10b} Numerous plastic procedures have been devised. The Wreden-Stone operation utilizes two fascial slings to encircle the anal canal which are anchored to the glutei maximi. Buie advocates a simple plastic procedure which consists of the excision of the scar tissue and the recreation of the original wound which was present immediately after fistulectomy.^{16a} Meticulous postoperative care results in a competent healthy scar. Blaisdell developed an ingenious and simple procedure which consists in isolating and reefing the external anal sphincter muscle thus decreasing the circumference of the whole muscle and the anal outlet.^{10c} Excellent results have followed the performance of this procedure. Knapp, in a selected case of incontinence, successfully utilized the superficial transverse perineal muscle for the repair.⁸²

Injuries of the Anus, Rectum and Sigmoid. Small particles of food and foreign bodies, such as fish bones, seeds, and so forth, may lodge in a crypt of Morgagni and result in infection of the crypt requiring surgical intervention. Foreign bodies lying free in the lumen of the rectum, such as enema tips, usually present no difficulties in their removal.

Impalement of the rectum is a serious condition. The prognosis

depends on the path of injury and the extent of visceral involvement. Immediate exploratory laparotomy is usually performed when perforation of a viscus has occurred. Expectant treatment and the performance of an occasional colostomy is indicated in extrarectal impalements with or without extensive perineal laceration.²⁸

Contrary to the general consensus, perforations of the rectum or sigmoid occurring during sigmoidoscopic examination may be treated conservatively, especially when the patient is a poor risk because of advanced age or concomitant disease, or in those instances where a delay in establishing a diagnosis has occurred.¹²²

Pediatric Proctology. As in the adult, proctosigmoidoscopic examination of infants and children is indicated in the presence of symptoms, such as bleeding, diarrhea, constipation, protrusion, tenesmus, or pruritus.^{33a, 115a} The presence of an obstructive lesion that prevents the insertion of the examining finger or the instrument into the anorectal outlet constitutes the only contraindication to sigmoidoscopy.

In infants and young children, the rectum is in a vertical position and the sigmoid may be long and tortuous with a sharp angulation either to the right or to the left of the pelvis; the bowel is very fragile and may be easily traumatized. Either morphine^{115a} or general anesthesia^{33a} is employed in most cases of infants or young children. However, in many children over 5 years of age, the examination may be carried out easily without the aid of either morphine or anesthesia. The employment of inflation of the bowel as an aid to sigmoidoscopy is a matter of personal preference and experience; it is considered safer to visualize the lumen of the colon before advancing the sigmoidoscope, which is best accomplished by gentle inflation. The original or a modified inverted position is considered the most suitable for sigmoidoscopy in infants and children.

Juveniles, like adults, are subject to inflammatory bacterial or parasitic disease, suppurations, fistulas and fissures *in ano*, prolapse of the rectum, benign and malignant polyps and other tumors. Unlike adults, infants and young children seldom have internal piles but more often present congenital malformations of the anus and rectum.

Miscellaneous Considerations. Clinical Pathology. The microscopic study of the bowel discharges at the time of proctosigmoidoscopy has become a routine procedure in many offices and clinics. The presence of cellular exudates in the bowel discharges is indicative of lesions associated with anatomic changes in the wall of the colon.⁸ The determination of the reaction of the feces is of importance.¹ The approximate pH of the feces can be established with the aid of nitrazene paper. Normal stool is acid in reaction.¹⁴³ The sedimentation time of erythrocytes is another simple office procedure.¹³⁹ The fact that the sinking of the red blood cells is accelerated in the presence of hidden suppurations in the anorectal tissues makes this test valuable in the differential diagnosis of acute anal pain and in the differentiation of an inflammatory reaction from a suppurative process following the injection of the long-acting anesthetics. The Frei test is at present performed routinely in all cases of diarrhea, rectal strictures and whenever the diagnosis is obscure.

Ambulatory Operative Treatment. Perianal hematoma (external thrombosed pile), subacute fissures and short subcutaneous sinuses or fistulas are suitable for ambulatory operative treatment.^{2, 18} The surgeon performing ambulatory operations for anorectal lesions should

provide adequate office facilities for immediate postoperative rest and care, and proper supervision at the patient's home.

It is generally conceded that the published good results of ambulatory operative treatment of proctologic lesions do not represent a fair cross-section of the work done throughout the country. That better results follow operations performed in a hospital can hardly be gainsaid;⁷² ambulatory surgical treatment is usually incomplete in scope and hence only palliative in character.

Sacrococcygeal (Pilonidal) Cysts and Sinuses. In spite of numerous studies there is still no unanimity of opinion as to the essential aspects of this lesion. Most investigators agree that the sacrococcygeal lesion is congenital in origin and that it arises from the ectoderm. They disagree as to whether nerve tissue or integument is the source of origin. The tendency to recurrence characterizes this lesion regardless of the form of surgical procedure utilized. Non-surgical procedures (injectational sclerosing therapy) are still on trial. The occasional concomitant occurrence of a malignant lesion⁵⁷ and postinjection sloughs favor clean-cut surgery.

Radiation therapy is advocated as a substitute for operation for the recurrence of infected sacrococcygeal sinuses.¹³⁸ It is conceivable that when all branches of the sinus and the ectopic epithelium are incompletely removed during the original operation, radiation therapy may fail, and reoperation may become necessary.

Rectal Bleeding. Bleeding from the rectum usually demands a complete survey to establish its source. Internal hemorrhoids are the most frequent cause while neoplasm is the most important. Profuse bleeding following the inexperienced injection of sclerosing solutions for the treatment of internal piles and prolapse occurs infrequently;¹⁷ the incidence of this complication cannot be surmised from the perusal of published reports. Blood originating from a lesion in the descending or sigmoid colon if retained in the rectum long enough may appear dark, resembling blood coming from a lesion in the upper intestinal tract or stomach, while, in the case of hypermotility of the intestines, blood coming from a gastric or duodenal lesion may occasionally be bright red. Rarely, bleeding in children may originate from an ulceration in a Meckel's diverticulum with or without aberrant gastric mucosa, or from an ulceration of misplaced gastric mucosa in the rectum.^{43,46}

Blood dyscrasias, such as thrombocytopenic purpura and vitamin C and K deficiencies may be the underlying cause in many cases of occult or gross bleeding from the colon and rectum. Bleeding noted in diarrheas is frequently an expression of subclinical hypovitaminosis and not necessarily caused by the inflammatory or infectious process of the bowel.⁹² Colonic bleeding noted in advanced Bright's disease and uremia may be due to vitamin K deficiency.²³

Effects of Irradiation on Rectum. Following radiation therapy (radium, Roentgen ray, or both) for malignant lesions of the urogenital tract there may develop changes in the rectum (as well as in other segments of the colon and small intestine) ranging from mild mucosal injury to ulcerations.^{136,149} The ulcerations may either erode the bowel wall and eventuate in perirectal suppuration or rectovaginal fistulas or terminate in healing with intense fibrosis leading to partial or complete stenosis. On the other hand, the perirectal structures may be primarily affected causing secondary involvement of the rectum. The

simple lesions may either be self-limited or may respond to conservative measures. The advanced lesions, *e. g.*, ulcerations or stenosis, may require temporary or permanent colostomy. The present consensus is against dilatation of the strictures because perforations are apt to follow this maneuver. Severe pain may be controlled by the resection of the presacral nerves.¹³⁶

Colonic Allergy. The reactions produced in the colon by allergy to foods have been experimentally demonstrated in humans to consist of edema, hyperemia and increased secretion.^{3,59,60} Histologically this reaction is represented by marked edema of the submucosa and cellular infiltration. These phenomena are produced partly by the direct contact of the offending food with the mucosa and, more importantly, by the allergen reaching the mucosa *via* the blood stream after absorption. Observations similar to the foregoing as well as spasm frequently encountered during proctosigmoidoscopy should suggest a possible allergic etiology and lead to further investigations.

Enterobiasis. The introduction of cellophane-tipped swabs constitutes a distinct advance in the study of pinworm infestations. Of equal importance is the therapeutic employment of the recently proposed enteric coated gentian violet.¹⁵⁴ This therapeutic agent is believed to be the most efficacious drug now available for the treatment of enterobiasis. While the treatment of individual patients has become relatively simple, the eradication of the pinworms occurring in several members of a family or in inmates of an institution is still a difficult problem.³⁴ This difficulty is caused by the high incidence of reinfection.

Acute appendicitis caused by *Enterobius vermicularis* is infrequently encountered. Occasionally several members of the same family may have pinworm infestation and acute appendicitis concomitantly.¹⁰³

Intestinal and Vaginal Trichomonas. Recent studies fail to support the common belief that trichomonads infecting the vagina are of intestinal origin. Experimentally, human and monkey vaginas cannot be infected with intestinal trichomonads.⁷⁵

Fecal Impaction. Fecal incontinence from accumulation of feces in the rectum occurs infrequently after operations; in the debilitated bedridden individual; following the use of barium sulphate for diagnostic purposes, or after the eating of roughage.^{7,106} The incontinence manifests itself as a continued discharge or diarrhea. The treatment consists of the administration of warm oil as retention enemata and the gentle digital removal of the impacted feces. Occasionally hydrogen peroxide enemata and the instrumental removal of the feces must be resorted to.

Mineral Oil. A recent provocative paper by Morgan deals with the misgivings on mineral oil.¹⁰⁹ Mineral oil is believed to interfere seriously with the physiology of defecation; it apparently causes the premature passage of feces from the transverse, descending and sigmoid colon, the true fecal reservoir, into the rectum. There the stool may be abnormally retained as the admixture of the oil with the feces prevents their complete evacuation. Mineral oil interferes with the healing of wounds following anorectal operations and may induce bleeding. Liquid petrolatum, by causing increased motility of the intestine and rapid transportation of food prevents its proper digestion and absorption and has a deleterious effect on the fat-soluble vitamins A, D and K.

Curtis and Kline³² found that the feeding of crystalline carotene in

vegetable oil to normal persons produces a rise of the concentration of carotene of the blood, and that a reversal of this effect occurs when mineral oil is fed with the carotene. They also demonstrated that the feeding of mineral oil 2 or 3 times daily before meals prevents the rise of the blood carotene following the partaking of a high carotene diet. However, no effect on the blood carotene occurs if the mineral oil is administered only before retiring when no food is ordinarily taken. This study shows that mineral oil mixed with food in the gastro-intestinal tract inhibits or prevents the absorption of carotene.

Gastro-intestinal Manifestations of Anorectal Lesions. As a rule, lesions of the anorectum produce a characteristic local symptom complex which is easily differentiated from that produced by disease in the upper digestive tract. However, in certain instances anorectal disease may cause referred abdominal symptoms suggesting disease of the stomach, appendix or the biliary tract. Recently, Gauss⁶⁴ called attention to the irritable colon and gastric irritation syndromes produced by disease in the anorectum (13 of his 15 patients responded promptly to proper proctologic therapy). The symptomatology of some of his patients included heartburn which occurred several hours after meals and was relieved by food or alkalies. Apparently the anorectal lesion produces irritation of the colon which in turn may produce the gastric irritation syndrome. This effect is mediated through the sympathetic and parasympathetic nerves of the autonomic nervous system.

Rectal Absorption of Sulfanilamide and Its Derivatives. Recent experimental studies proved that sulfanilamide is absorbed from the rectum and colon in man when administered either in solution^{141a} or in suppository.^{141b} The concentration of sulfanilamide in the blood after the suppositories was inadequate, but the solution gave a concentration comparable with that resulting from the oral administration. The rectal route of administration of sulfanilamide is recommended whenever the oral route cannot be utilized. The same total dosage may be employed for the rectal as for the oral administration. The rectal route has been employed successfully in the treatment of anorectal manifestations of venereal lymphogranuloma⁹⁵ and in chronic ulcerative colitis^{27,141b} (Protocol 4).

The rectal administration of sulfapyridine in suspension has been employed successfully in the treatment of pneumococcal pneumonias.¹⁵⁰ The dosage required to produce an adequate concentration of sulfapyridine in the blood was 3 times larger than the oral dose. Nausea was almost eliminated.

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OPHTHALMOLOGY.

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TREATMENT OF THROMBOSIS OF THE RETINAL VEINS.

THROMBOSIS of the central vein of the retina or one of its branches or tributaries is a rather frequent cause of loss of vision in middle aged or elderly individuals. Its frequency is considerably greater among patients with relatively benign hypertensive disease than it is in the general population or in patients with severer forms of hypertensive disease. The majority of patients who present themselves with loss of vision due to thrombosis of a retinal vein are in other respects in relatively good physical condition; so that the loss of vision is their primary concern. The average age of occurrence of this type of vascular accident is 57 years, so that many of these patients have the expectancy of a number of years of active life. It would seem, therefore, that any form of treatment would be worth while which would offer a chance of restoring useful vision to the affected eye. In the past, little has been offered to these patients in the way of treatment other than general measures for the control of the hypertensive disease, if present, and potassium iodide. However, in 1930, Löwenstein and Reiser⁸ suggested Roentgen ray therapy to the affected eye, and, in 1938, Holmin and Ploman⁶ reported the use of heparin in the treatment of a case of thrombosis of the central vein of the retina. Though reports of the results of these two types of therapy have been rather few to date, it was thought that it might be of interest to compare the visual results obtained with those in essentially untreated cases.

In a series of 26 cases of thrombosis of a tributary retinal vein reported by Moore in 1924, the last recorded vision was 6/60 or less in 14 (54%), between 6/36 and 6/12 in 10 (38%), 6/6 in 1 (4%) and unrecorded in 1. Considering only the 12 cases in which vision was recorded at least 1 year after the occurrence of the thrombosis, the final visual acuity was 6/36 or less in 8 cases (67%), between 6/24 and 6/12 in 3 (25%), and 6/6 in 1 (8%). In a similar series of 29 cases reported by Jensen⁷ in 1936, visual acuity at the end of a year or longer was 6/36 or less in 14 (49%), between 6/24 and 6/12 in 9 cases (31%), 6/9 in 3 (10%), and 6/6 in 3 (10%). Combining these two series, it is apparent that useful vision was obtained or retained in 19 of 41 cases (46%) and normal vision in 4 (10%). Secondary glaucoma did not develop in any of the 31 cases of thrombosis of a tributary retinal vein reported on by Moore.¹¹ It developed in only 1 of a series of approximately 50 cases reported on by Uhthoff, and in only 1 of Jensen's 54 cases.

The final acuity of vision obtained in untreated cases of thrombosis of the central vein is usually considerably poorer than it is in cases of thrombosis of tributary veins. Thus, among the 19 cases with records of vision in Moore's series, the last recorded vision was 6/60 or less in

17 (90%), 6/36 in 1 (5%) and 6/24 in 1 (5%). Among the group of 10 cases which were observed for more than a year, the last recorded vision was less than 6/60 in all. So that useful vision was not obtained or retained by any patient in this group. Secondary glaucoma developed in 10 of Moore's 31 cases of thrombosis of the central vein (32%), and in 12 of Uhthoff's 50 cases (24%).

Stimulated by a report of Hessberg's on rapid and complete absorption of hemorrhages in the retina following irradiation of the eye, Löwenstein and Reiser⁸ decided to try the effect of medium and small doses of Roentgen ray on thrombosis of the retinal veins. They thought originally that the rays might have a direct thrombolytic action and that they might stimulate the formation of collateral circulation. Later, however, they decided that these two effects could not be demonstrated. They concluded that the essential effect of the Roentgen rays was that of vasodilatation by which an active hyperemia was produced which increased the rate of absorption of the hemorrhagic extravasations. They thought also that the increased vis a tergo resulting from the vasodilatation would prevent the thrombus from becoming completely occlusive if it were not so originally. They suggested also that Roentgen ray therapy might prevent the development of secondary glaucoma by decreasing the secretion from the ciliary body. They reported 1 case of thrombosis of the central vein in which the vision was 6/20 at the time treatment was started. One year later the vision was 6/5. Also, in a case of thrombosis of a tributary vein the vision, which had been 6/20 at the onset, was 6/4 at the end of 4½ months.

Löwenstein and Reiser thought that irradiation of the eye was indicated especially in cases in which a specific tuberculous or syphilitic affection of the intima of the vein was the basic cause of the thrombosis. They expressed doubts that this method of treatment would be of any value in cases of thrombosis of the central vein in which the obstruction was caused primarily by thickening of the connective tissue in the lamina cribrosa or in cases of tributary vein thrombosis in which the obstruction resulted from compression of the vein by a sclerosed arteriole.

In 1932, Schnyder and Forster¹⁶ reported on the treatment of 7 cases of thrombosis of retinal veins by irradiation according to the method of Löwenstein and Reiser but using somewhat smaller doses. Two of the cases showed complete thrombosis of the central vein. In 1 of these, only slight residuals were visible ophthalmoscopically after 6 months and the vision was 6/10. In the other, the hemorrhages were completely resorbed after 8 months and the vision was between 6/10 and 6/12. There were 3 cases of thrombosis of a tributary of 1 of the main temporal veins without much disturbance of vision. At the end of 3 months all the hemorrhages had been resorbed in 2 of these cases and most of the hemorrhages in the other. In 1 case the main superior temporal vein was thrombosed and there were extensive hemorrhagic extravasations involving the macula. At the end of 5 months, only a few residual hemorrhages were present and the vision was between 6/12 and 6/10. The seventh patient had had a thrombosis of the superior temporal vein of the right retina 3 years previously. The hemorrhages had been completely resorbed after 27 months, but as a result of consecutive retinal and optic nerve atrophy the vision remained

reduced to ability to count fingers at 2 meters. When thrombosis occurred in the superior temporal vein of the left retina, the eye was irradiated. The hemorrhages were almost completely resorbed at the end of $5\frac{1}{2}$ months and the vision was between 6/12 and 6/10. The results in this series would seem to be considerably better than the average obtained in the untreated cases.

Schnyder and Forster stated that, in all 7 cases, they had the impression that as a result of the Roentgen ray therapy the hemorrhages absorbed considerably more rapidly and completely than was usual in cases of thrombosis of the retinal veins. They noted that in 2 cases, 1 of central vein and the other of tributary vein thrombosis, venous thrombosis with hemorrhages and detachment of the retina developed in the periphery of the retina some time after the irradiation therapy had been concluded. In both of these cases spontaneous healing took place, but Schnyder and Forster thought that the lesion was caused probably by a tear of the retina resulting from the hyperemia and consecutive edema produced by the irradiation. Therefore, they were inclined to think that the treatment was not entirely harmless and that it should be reserved for those cases in which the completeness of the thrombosis and the extent of the hemorrhages make the prognosis for recovery of vision doubtful if the condition is untreated.

Later reports on the results of irradiation treatment have not been so encouraging. In a discussion at the 1936 meeting of the German Ophthalmological Society of Czechoslovakia, Braun³ and Ascher¹ stated that Roentgen therapy did not seem to influence the course of cases of complete thrombosis of the retinal veins though it might have a favorable effect on cases of partial or incomplete thrombosis. In 1937, Gradle⁵ published the results obtained by irradiation in a series of 16 cases. He was particularly interested to see if this type of treatment was of any value in preventing the development of secondary glaucoma, a point which had not been considered by the other authors. He used 3 to 6 exposures of filtered rays up to the extent of one-fourth to one-third of a skin erythema dose. He did not use pilocarpine as a prophylactic in this series. The results obtained were compared with those in a series of 21 untreated cases which had been observed over a similar period of time. Pilocarpine was used as a prophylactic against the development of secondary glaucoma in the cases of thrombosis of the central vein in this second group. The cases in each group were observed over periods ranging from several weeks to 10 years.

Among a group of 14 cases of thrombosis of a tributary vein in which irradiation was not used, the vision at the time of the last examination was 6/30 or less in 7 (50%), 6/12 to 6/10 in 6 (43%), and 6/5 in 1 (7%). Among a group of 7 cases of thrombosis of a tributary vein in which irradiation was used, the vision at the last examination was 6/30 or less in 5 (72%), 6/20 in 1 (14%) and 6/5 in 1 (14%). Among a group of 7 cases of thrombosis of the central vein in which irradiation was not used, the vision at the last examination was 6/30 or less in 6 (86%) and 6/6 in 1 (14%). Among a group of 9 cases of thrombosis of the central vein in which irradiation was used, the vision at the last examination was 6/30 or less in 7 (78%) and 6/15 in 2 (22%). Essentially, then, the final vision obtained differed very little in the two groups of cases. Irradiation was not entirely successful either in the prevention or the development of secondary glaucoma. Glaucoma developed in

1 (7%) of the untreated cases of tributary vein thrombosis and in 1 (14%) of the untreated cases of central vein thrombosis. In both of these cases, the glaucoma was bilateral and was of the chronic simple or compensated type and may have developed independent of the thrombosis. Glaucoma did not occur in any of the 7 cases of tributary vein thrombosis which were irradiated, but typical acute uncompensated glaucoma developed in 1 (11%) of the 9 irradiated cases of central vein thrombosis.

In summary, Gradle stated that he did not think that irradiation accelerated the absorption of the hemorrhages or that it improved the end result so far as vision was concerned. He expressed the opinion that irradiation might be of some value in the prevention of secondary glaucoma.

In view of the rather conflicting reports on its efficacy, Roentgen ray treatment may be worthy of further trial in the treatment of retinal venous thrombosis. I regret that a rather extensive report on this method of treatment which was published in *Ophthalmologica* for June-July, 1940, is not available to me for review at the present time.

In March, 1938, Holmin and Ploman reported the results obtained in a case of thrombosis of the central vein of the retina which they treated with heparin. The vision shortly after the onset of the thrombosis was 6/30. Heparin therapy was started 41 hours after the onset. Three to four daily doses of 1.66 mg. per kilo of body weight were given during a period of about 10 days. The ophthalmoscopic picture did not change materially during the time of administration of the heparin but the vision improved to 6/7. During the following weeks the hemorrhages absorbed gradually. At the end of 3 months the vision was 6/6.

Ploman¹³ had studied previously 13 cases of thrombosis of the central vein. Nine of these had become blind, 8 from secondary glaucoma, 1 from proliferating retinitis and detachment of the retina. Final vision in 1 was hand movements, in 2, 6/60, and in 1, 6/20.

In Ploman's opinion, the obstruction to the bloodflow in the case treated with heparin was not complete at the time he saw the patient. In most cases, he thinks, clots accumulate on the thrombus and finally produce complete obstruction. Heparin prevents this further growth of the thrombus and permits retraction of the fibrin already present in the clot so that the obstruction to the circulation is reduced. Ploman thinks also that the heparin may diffuse through the capillary walls and into the tissues so that they become heparinized. As a result, the blood in the hemorrhagic extravasations in the retina remains more liquid and can be resorbed more rapidly.

In July, 1938, Boström and William-Olsson² reported a second case of thrombosis of the central vein of the retina treated with heparin. The heparin was not started in this case until about a month after the occurrence of the thrombosis. Vision at the time of first examination was 6/60. Heparin was given intermittently for 20 days. At the end of 1 month the retinal lesions had improved considerably and vision was 6/10. In discussing the rationality of the treatment, the authors stated that in intravascular thrombosis the thrombus acts as a foreign body, producing kinase and a tendency to coagulation in its neighborhood. Heparin lessens the tendency to coagulation. This prevents growth of the thrombus and allows the coagulum to retract so that

parietal canalization may occur. Later the thrombus itself may be dissolved by proteolytic enzymes.

In June, 1938, Ploman reported his further experiences with heparin treatment of thrombosis of retinal veins. He used, in hospital cases, a daily dose of 250 mg. divided into 4 doses and, in out-patients, 200 to 300 mg. daily in 2 doses. Treatment was continued for from 5 to 10 days. Two additional cases of central vein thrombosis were treated. In 1 of these at the end of 3 weeks the ophthalmoscopic appearance was considerably improved and vision had increased from hand movements to finger counting at 4 meters. In the other, after 6 weeks' treatment with potassium iodide, vision had decreased from 6/8 to 6/9. One month after 3 days of heparin treatment the vision was 6/6. He treated also 6 cases of tributary vein thrombosis. In 1 of these there was no improvement, and the vision was still 6/60 at the end of 6 weeks. In another, vision improved from 6/20 to 6/9 in 2 weeks, but 1 week later a second thrombosis occurred which reduced the vision again to 6/20. Heparin did not help this second thrombosis. In the other 4 cases, improvement was noted. The final recorded vision was 6/20 in 2 cases, 6/10 in 1, and 6/9 in 1. The period of observation in these cases was rather short, 6 weeks or less in all but 1 case. For comparison, Ploman gave the results at the end of 3 months in 26 cases of tributary vein thrombosis treated with potassium iodide. Among these 26 cases, 4 were worse, 12 were unchanged and 10 were improved. The mean improvement in vision was 0.2. The mean improvement in vision in heparin treated cases was 0.3. Ploman admitted that the period of observation in these cases was too short to permit any conclusions as to final results.

Ploman used heparin in the treatment also of 1 case of hemorrhage in the retina (type not stated) in which the vision improved in 2 weeks from 6/15 to 6/6, and in 1 case of hemorrhage into the vitreous in which the vision improved from counting fingers at 2 meters to 6/7 in 1 month.

In April, 1941, Rea¹⁴ reported the heparin treatment of 3 cases of complete thrombosis of the central vein and of 2 cases of tributary vein thrombosis. He stated that one of the eyes with central vein thrombosis became glaucomatous and completely blind. Some improvement was noted in the 2 other cases. In 1 case, vision improved from 2/60 to 6/24. The 2 cases of tributary vein thrombosis were completely cured with vision of 6/6. Rea thought that the treatment produced good results if it was started the same day as the occurrence of the thrombosis or "immediately afterward;" but that, when there was a delay of several days in starting the heparin, the results were not good.

At the 1940 meeting of the American Ophthalmological Society, MacDonald⁹ reported the results obtained by the use of heparin in 1 case of thrombosis of the central vein of the retina and in 1 case of thrombosis of the macular branch of the superior temporal vein. In the case of central vein thrombosis, treatment was started 2 weeks after onset when vision was ability to count fingers at 2 meters. Heparin was given by the continuous drip method and the clotting time was kept at or above 30 minutes for 5 days. At the end of 6 months, vision was 4/36. Numerous punctate hemorrhages were present in the retina. In the case of tributary vein thrombosis treatment was started 3 months after the onset of the thrombosis when vision had decreased from 6/36

to 6/60 and the hemorrhages had increased in number. Heparin was given by the continuous drip method and the clotting time was kept at or above 20 minutes for 5 days. At the end of 6 weeks vision was 6/18 and no new hemorrhages had occurred.

In the discussion of MacDonald's paper Gifford⁴ stated that he had treated 2 cases of thrombosis with heparin without improvement in vision. Treatment was started 1 month and 2 weeks after the occurrence of the thrombosis, respectively. Rychener¹⁵ reported on 5 cases of thrombosis of the central vein; heparin was given intermittently (without laboratory control of the clotting time) in 1, and by the continuous drip method in the other 4, the clotting time being kept at approximately 15 minutes. The final vision obtained was less than 6/60 in 4 cases, and 6/20 in 1 case. He treated also 2 cases of tributary vein thrombosis. Final vision was 6/10 in 1 case and 6/6 in the other.

In his paper, MacDonald called attention to the apparently spontaneous cure of an occasional case of thrombosis of the central vein in a young individual. He mentioned cases reported by Mathewson¹⁰ and by Parker¹² in which 6/6 vision was regained in 1 year and 16 months respectively. In the discussion Verhoeff¹⁷ stated that, in his opinion, most cases of so-called "thrombosis of the central vein" in elderly individuals are really obstructions of the vein caused by obliterating endophlebitis and that actual thrombosis occurred only rarely and then in young individuals. I am inclined to think that either of these types of occlusion of the vein may occur without any definite age limitations and that the prognosis is relatively good in the cases of true thrombosis and essentially hopeless in the cases of obliterating endophlebitis or phlebosclerosis. If a differential diagnosis between these two types of lesion could be established clinically, the indications for the use of heparin would be more clearly defined and, perhaps, the results of treatment in selected cases would be more uniform.

TABLE 1.—VISUAL RESULTS IN THROMBOSIS OF THE CENTRAL VEIN OF THE RETINA.

	No. of cases.	Vision.		
		6/30 or less.	6/20 to 6/10.	6/7 to 6/6.
Untreated	42	36 (86%)	2 (5%)	4 (9%)
Irradiation	12	7 (58%)	4 (33%)	1 (9%)
Heparin	14	8 (58%)	3 (21%)	3 (21%)

Reference to Tables 1 and 2 will show that, though the number of treated cases is rather small, there does seem to be a definite improvement in the visual end results with either irradiation or heparin therapy with the results a little in favor of the heparin. Thus, in cases of central vein thrombosis, vision of 6/20 or better was obtained in only 14% of the untreated cases, in 42% of the irradiated cases, and in 42% of the heparin treated cases. In the cases of tributary vein thrombosis, vision of 6/20 or better was obtained in 49% of the untreated cases, in 62% of the irradiated cases, and in 91% of the heparin treated cases.

TABLE 2.—VISUAL RESULTS IN THROMBOSIS OF TRIBUTARY RETINAL VEINS.

	No. of cases.	Vision.		
		6/30 or less.	6/20 to 6/10.	6/7 to 6/6.
Untreated	68	35 (51%)	28 (41%)	5 (8%)
Irradiation	13	5 (38%)	3 (24%)	5 (38%)
Heparin	11	1 (9%)	7 (64%)	3 (27%)

McCullough, of Toronto, has told me personally of favorable results in cases of retinal vein thrombosis treated with heparin. Personally, I have observed recently a case of thrombosis of the central vein treated with heparin in which the hemorrhages had been completely absorbed from the retina within 6 months after the onset, and vision had returned to 6/6. In fairness, however, I should state that during essentially the same period, another case of thrombosis of the central vein cleared up completely under treatment only with potassium iodide and vision of 6/6 was regained in this case also. On the basis of the results reported so far, it would seem well worth while to try these methods of treatment in cases of thrombosis of either the central or a tributary retinal vein if the case is seen reasonably soon after the occurrence of the thrombosis.

HENRY P. WAGENER, M.D.

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THE
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SEPTEMBER, 1941

ORIGINAL ARTICLES.

UNUSUAL SYMPTOMATOLOGY WITH TUMORS OF THE CEREBELLUM BASED ON 158 VERIFIED CASES.

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THE diagnosis of the presence of a tumor of the cerebellum presents few difficulties in the typical case. However, in the absence of characteristic neurologic signs, localization may be uncertain. The obscure case of cerebellar tumor may be attended by unexpected complications for which the surgeon may be totally unprepared. This report proposes to call attention to unusual cerebellar symptomatology and findings which are emphasized in order to clarify diagnosis of the atypical case. The unusual rather than the usual findings have determined the pattern of this report.

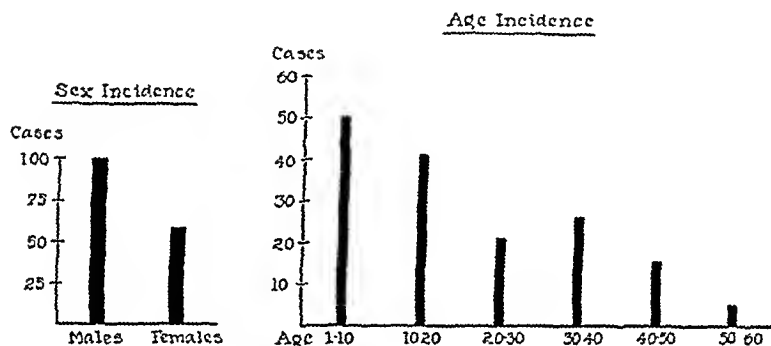
The point may be raised that final decision in a questionable diagnosis of tumor of the cerebellum rests upon results of ventriculographic study. This is unquestionably true in most instances. However, it is equally true that the interpretation of the ventriculogram is aided by an appreciation of all clinical possibilities. Also, doubtful pneumographic findings occur, and frequently in the clinically puzzling cases.

The material presented includes the diagnostic findings present in 158 cases of verified tumor of the cerebellum. The review is summarized graphically where possible. A number of findings required a more detailed analysis. These will be considered and, when pertinent, illustrated by case reports.

Summary of Findings. *Convulsions.* Motor convulsions were present in 21 and attacks of loss of consciousness occurred in 13 cases.

making a total of 34 instances of the convulsive state (21.5%). In 11 instances the lesions, in this group of patients, was in the midline; in 22, in the right or left lobe of the cerebellum. In 1 case the tumor was reported as invading both cerebellar lobes. Papilledema was present in greater or in less degree in 31 cases. One patient had no papilledema; in 2 there was no record of the fundus examination. The manifestations of the convulsive state were as follows:

Type	TYPE OF CONVULSIONS	Instances	Autopsies
Segmental—clonic	7	3
Generalized:			
Clonic	3	3
Tonic	11	4
Syncopal	13	3



Duration of Symptoms to Time of Operation

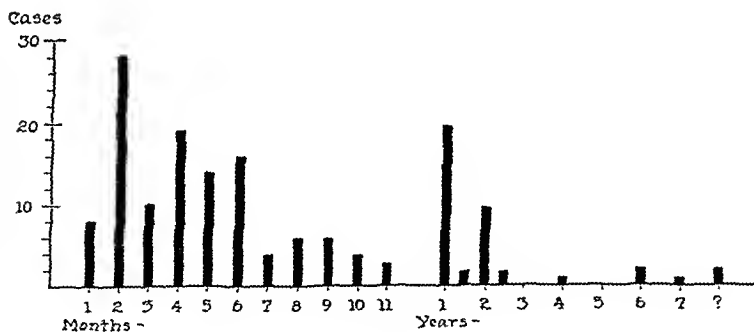


CHART 1.

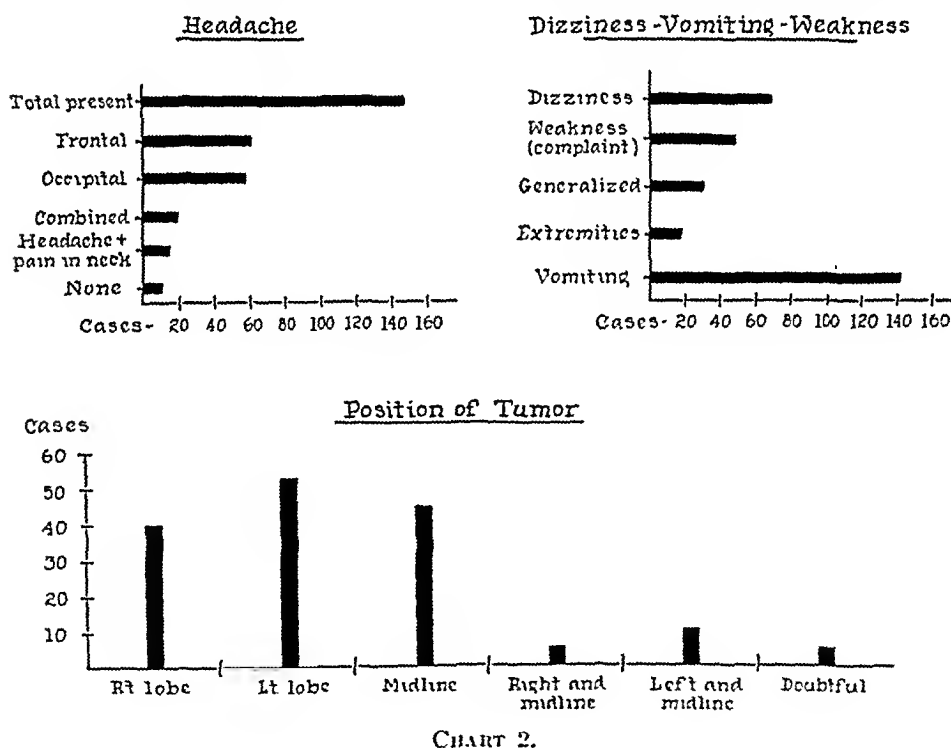
Syncopal attacks which occurred commonly in an early or middle period of the patient's disease may be illustrated by the following instance:

CASE 1.—A 25-year-old woman, complained of pain in the right ear, headache, unsteadiness of gait and numbness of the right side of the face in

April, 1925. Symptoms were first noticed in October, 1923, when she experienced pain in the back of the head and in the neck. In February, 1925, the patient noticed difficulty in walking and impairment of vision in the right eye. In March, unsteadiness of gait increased. She had twitching of the muscles of the right side of the face and lips. During this month also she had fainting attacks which occurred 4 to 5 times daily. During the attacks which lasted about 1 minute, she was unconscious and became cyanotic. Recovery was rapid as profuse perspiration occurred. Neurologic examination showed the patient to be hypotonic. Three diopters of papilledema were present in the right eye and 2 in the left. Incoördination could not be demonstrated in the extremities although the patient tended to fall to the right in gait testing. Horizontal nystagmus was present on lateral gaze; there was a weakness of the right side of the face. At operation, a cyst of the right lobe of the cerebellum was evacuated.

An example of the clonic-segmental type of convulsion is shown by the following case which is described in brief:

CASE 2.—A 38-year-old male carpenter, was well until December, 1930, when he began to vomit. In April, 1931, headache followed upon attacks of vertigo. At this time, also, the patient began to have spells of shaking in both upper extremities. The tremors were rapid and coarse occurring every



2 days. Examination the following month showed a mentally dull patient who held his head in pain. There was a moderate hypotonia of the left upper extremity; finger-to-nose testing showed a slight ataxia and dysmetria of the right upper extremity; rapidly alternating movements were impaired in both hands. The patient was unable to raise himself from the dorsal decubitus position without the use of the arms. Reflexes were pendulous in the lower extremities. There were 2 diopters of papilledema present.

Nystagmus was absent. While being examined, the patient had "mild, fairly rapid, pseudo-clonic jerkings of the shoulder girdle muscles, the muscles of the arm and forearm lasting for 30 seconds. There was no typical distribution of the clonic contractions. They were not the usual flexor type seen in cortical irritation and they caused no regular pattern of movement of the extremities. Palpitation of the muscles during the convulsions indicated that the contractions were more of the nature of a clonic affair than a tremor." Routine Roentgen studies were normal. A ventriculogram was recommended to localize the lesion. The patient was given a colonic irrigation because of constipation and because an enema was considered unwise in view of the unknown localization of the tumor. After an hour of irrigation, the patient was described as the picture of shock. At this time Dr. Charles H. Frazier saw him have "a definite clonic convulsion of his upper extremities." Death occurred 12 hours after a ventricular trephine. Autopsy showed a pronounced hydrocephalus with a pressure cone and a right cerebellar cyst.

Visual Field Defects. Significant and confusing alterations in the visual fields were found to be present in 8 cases. Reliance placed upon the perimetric examination as a diagnostic aid served to make the occurrence of such defects a false localizing sign of major importance. The defects were classified as follows, some of which are demonstrated in Figure 1: Homonymous hemianoptic defects, 4; bitemporal hemianoptic defects, 1; unclassifiable, 3.

Case 3 demonstrates how such a finding may confuse the diagnosis.

CASE 3.—The patient was a 54-year-old male. A year before admission, he noticed a dull ache in the back of his neck. This became increasingly severe. Four months before admission, his gait became unsteady. Irritability and failing memory with drowsiness then became outstanding complaints. The neurologic examination was inconclusive insofar as furnishing localizing information. There were marked mental disturbances and questionable aphasic manifestations. Roentgen examination of the skull showed the pineal body calcified and in the midline. The optic disks were normal except for the presence of a small flame-shaped hemorrhage in the right retina. The visual acuity seemed normal to the examiner although no visual notations were made. Perimetric examination revealed the presence of a right homonymous hemianopsia. Although the available findings suggested a lesion either in the occipital or temporal lobe, the lack of evidence of increased intracranial pressure made pneumographic studies necessary for precise diagnosis. Ventriculography showed a marked symmetrical dilatation of the ventricular system. In view of this, a suboccipital craniectomy was performed. A cystic hemangioma was found in the left cerebellar lobe.

Other Ophthalmologic Findings. Papilledema was present in 126 instances and absent in 15. In the remaining 17, the finding was not recorded or was equivocal. Of the 15 cases in which papilledema was absent, 3 were 13 years old and the remainder were in the age group of 20 to 41. The survey Roentgen examination in this group was negative in 9 cases. In 7, ventriculograms were made and all showed hydrocephalus. In 2, unsatisfactory encephalograms were done. The onset of symptoms in the group showing no papilledema dated from 2 weeks to 1 year before admission. In 2 cases the

patients died unexpectedly, 1 in spite of emergency surgery. Although papilledema was absent, hydrocephalus was found either by ventriculography or autopsy in 9 cases.

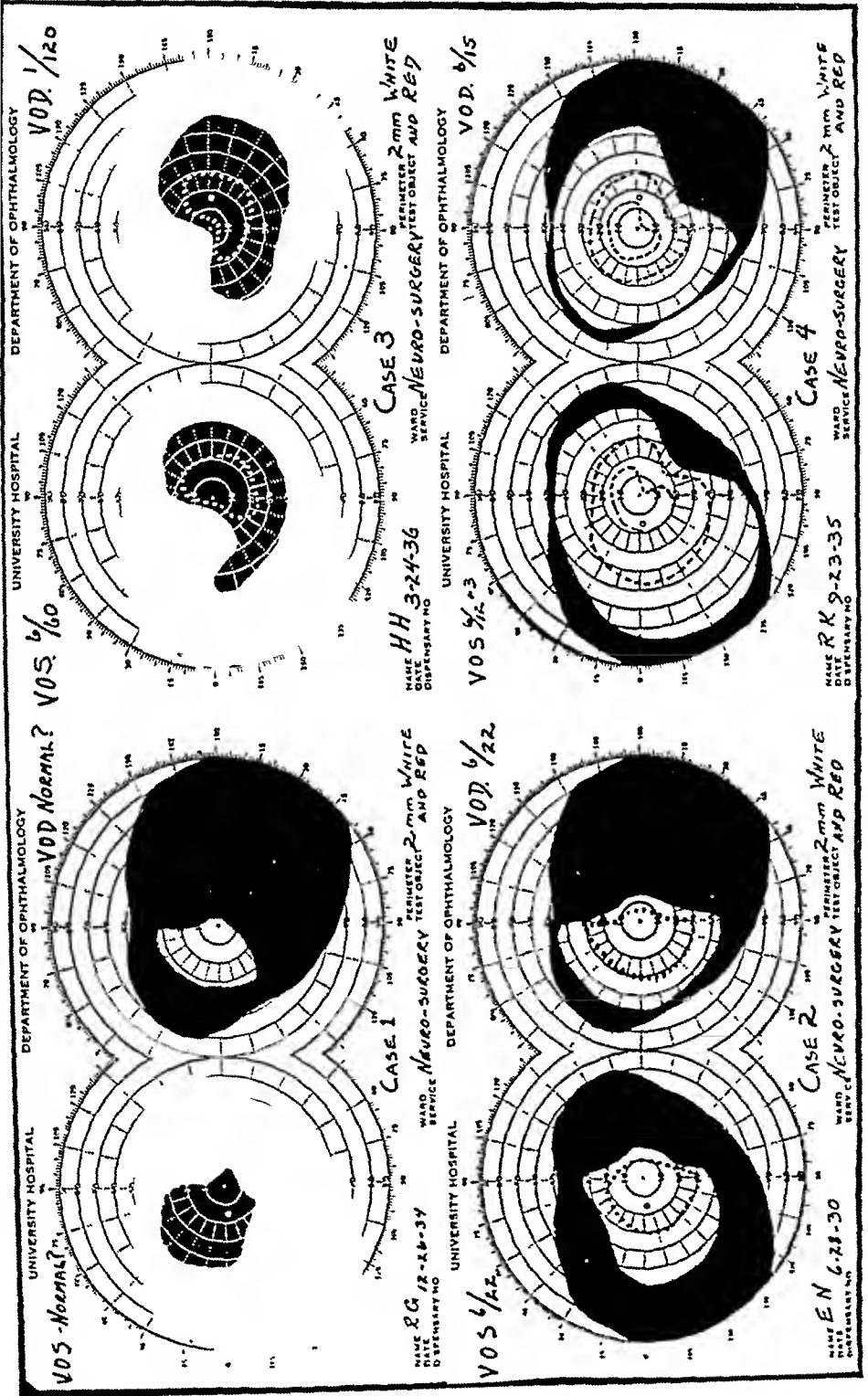


Fig. 1.—Representative visual field charts of a group of 8 patients showing confusing defects.

The complaint of impaired or failing vision was common, being present in 50% of the cases. In 6 instances, this complaint was present in the absence of papilledema. Eleven patients were blind in both eyes; 3 had unilateral loss of vision on admission. Three of

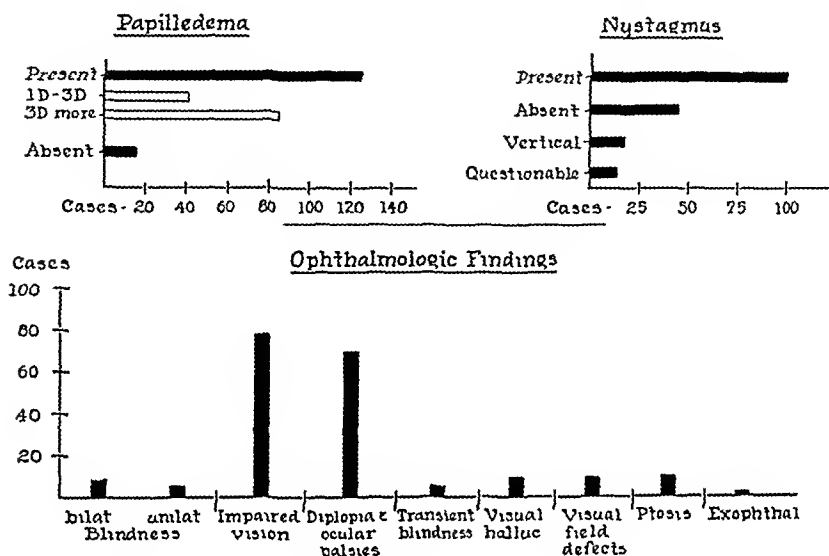


CHART 3.

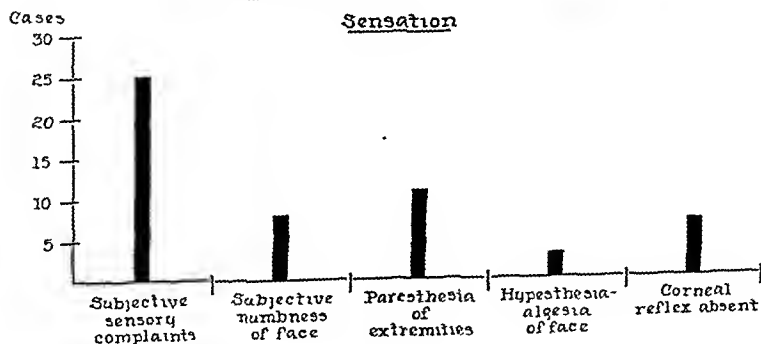
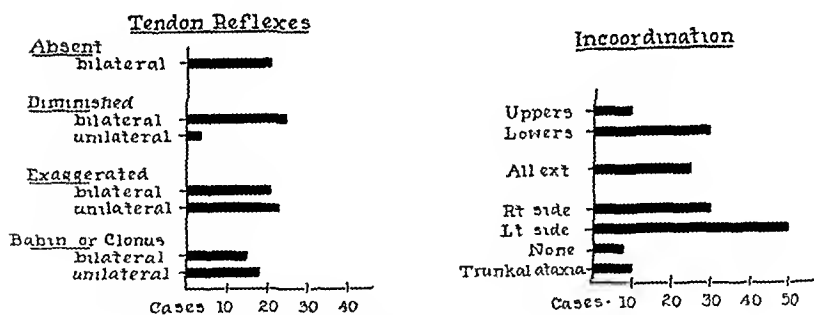


CHART 4.

the 11 patients who were completely blind at the time of admission had rapid loss of vision through a period ranging from 8 weeks to 3 months which was associated with marked papilledema. Two patients had sudden, complete loss of vision. None of the group, who was blind on admission, recovered sight.

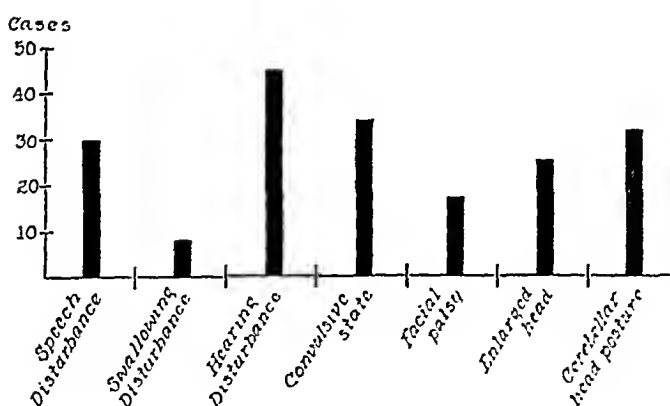
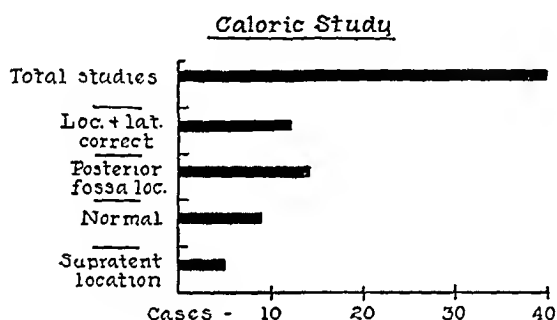
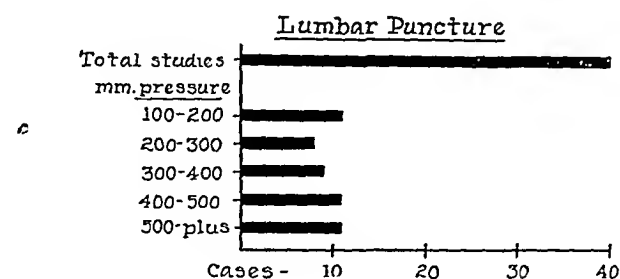


CHART 5.

Transient attacks of blindness occurred in 5 patients. This was always a late symptom. One of these patients described frequent attacks of blindness. About once an hour she became "stone blind for 2 or 3 minutes." Between attacks she thought her vision normal. (Measurement of acuity was 6/9 02.) Papilledema of 5 diopters was present.

Visual hallucinations were complained of by 8 patients. The hallucinations were described as follows:

1. Saw different colors before eyes.
2. Saw wild cherries, grapes, haystacks and fires burning.
3. Saw streaks before eyes which were dark during the day and light at night; at night frequently saw balls of light before the eyes.
4. Hallucinations wherein the patient stopped his truck thinking that he had seen a bad accident.
5. Had hallucinations of formed images of men and autos.
6. Saw scotomata and shadows.
7. Saw scotomata early; this was followed by subjective images of dogs, cats, mice, bugs, spiders, light flashes.
8. Saw light flashes and subjective images.

All these 8 patients noted concomitant impairment of vision. Advanced papilledema was present in each.

It is noteworthy that 11 patients had third nerve palsies, in 2 instances bilaterally. In 1 case this finding led to an incorrect supratentorial exploration.

The majority of cases showed nystagmus. In 41 instances, however, this sign was absent. Moreover, incoördination was absent in 8 members of this group and reported as minimal in 4. All except 2 of the 41 cases showed evidence of increased intracranial pressure either by Roentgen study or by the presence of papilledema. A right or left lobe tumor was present in 29; a midline tumor in 12.

Vertical nystagmus was observed in only 18 patients. In 17 cases of the 18 horizontal nystagmus was also present. A midline tumor was found in 12 of these patients while in 6 the lesion was located in either cerebellar hemisphere.

Lumbar Puncture. Lumbar puncture was performed in 50 cases. It is noteworthy that in 11 the spinal fluid pressure was within normal limits (100 mm. to 200 mm. of water). In these 11 cases papilledema was absent in 4. The remaining 7 showed variable degrees of papilledema.

Roentgenographic Studies. In 108 cases a survey roentgenologic study was made. Two-thirds of these studies were reported negative. Approximately one-third of the cases showed Roentgen evidence of increased intracranial pressure. Other qualified diagnoses in addition to increased intracranial pressure signs were as follows:

Calcification in the tumor mass	2
Rarefaction in bone overlying the lesion	3
Petrous ridge erosion	3
Parasellar lesion in right middle fossa	1

Ventriculography was performed in 37 cases. In a number of instances, ventricular estimations were carried out. The finding of bilaterally enlarged ventricles, in the latter procedure, precluded the necessity of air injection. An internal hydrocephalus was ob-

served in 21 of the 37 studies. In 2 cases, the diagnosis of "top normal" ventricles was made. A supratentorial localization was incorrectly made in 5 cases. Two other patients were diagnosed as having third ventricular tumors. Lateral ventricular defects were noted in 5 cases; in 2 of these a defect was present in the body of one ventricle; in 2, a unilateral posterior horn deformity was diagnosed and in one there was asymmetry of the lateral ventricles. Three cases showed defects in the fourth ventricle, one accompanied by hydrocephalus.

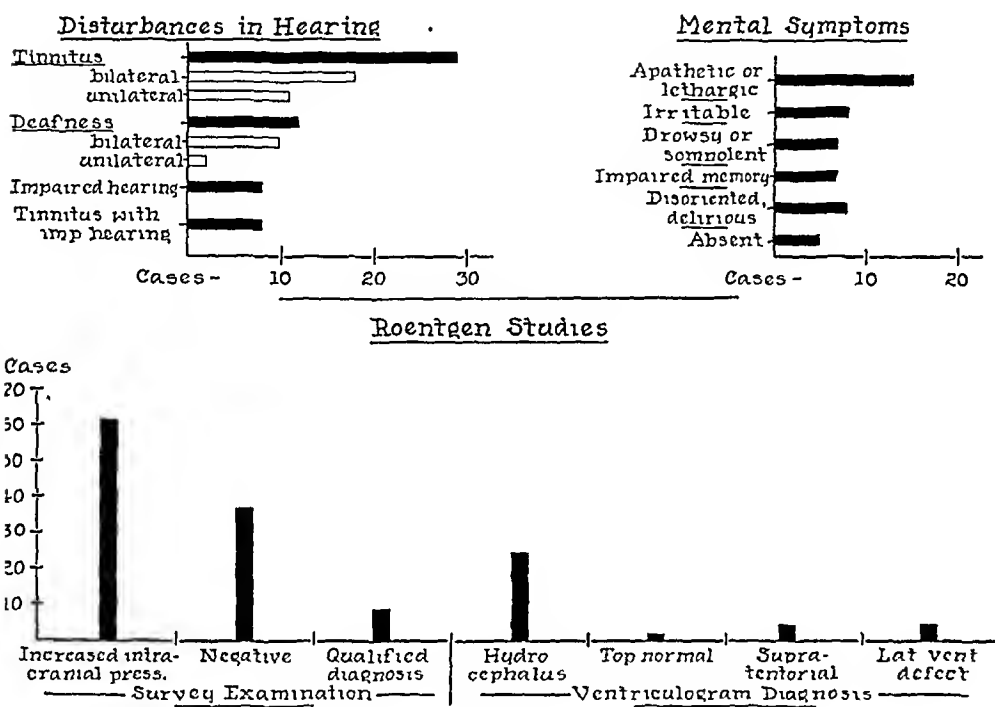


CHART 6.

Sensory Phenomena. Sensory complaints and signs were not rare. Numbness of the face was complained of by 8 patients. Paresthesias including the tongue, arm, hands, trunk, fingers and lower extremities were noted in 11 cases. Anesthesia of one cornea was present in 7 instances. Questionable findings upon the latter point were excluded. Objective impairment of sensation in the remaining distribution of the fifth nerve was observed in 3 of the 7 patients. Four members of this group also had facial palsies.

Caloric Examination. In 14 cases the caloric examination failed to indicate the presence of posterior fossa tumors which were subsequently found. In 5 instances the examination was misleading, suggesting a supratentorial lesion. Review of these cases failed to suggest any correlation of findings to account for the results of the examination.

Tendon Reflexes. The tendon reflexes did not appear to conform to a uniform pattern. In the majority of cases, the tendon reflexes were normal. Exaggerated reflexes, either unilateral or bilateral, were encountered in 44 cases, while in 33 clonus or an extensor plantar reflex was elicited.

Cranial Nerve Palsies. A facial palsy was definitely reported in 17 cases. In 19 a slight facial palsy was recorded, and in 6 others this sign was indicated as being questionable. Symptoms referable to the eighth nerve were present in 57 patients. Deafness or impaired hearing was present in 28 cases and tinnitus was complained of by 29. Four cases presented the syndrome of the cerebello-pontine angle, having palsies of the 7th, 8th and 5th nerves. In each instance, no compression of the nerves could be visualized at operation. In addition, 6 cases showed involvement of the 7th and 8th nerves and 3 of the 7th and 5th.

Discussion. The diagnosis of tumor of the cerebellum is both aided and complicated by the development of a rapid and early hydrocephalus which results from the strategic position of the tumor. Although increased intracranial pressure is characteristic of the cerebellar syndrome, false localizing signs may arise from the secondary hydrocephalus produced. As a result, early focal signs may be lost or overshadowed by prominent secondary effects. Collier⁴ drew attention to the occurrence of false localizing signs due to increased intracranial pressure. He concluded that in the presence of advanced tumor of the brain with hydrocephalus, focal signs lost importance.

It has been suggested that false localizing signs due to increased intracranial pressure and hydrocephalus are cerebellar in character. Nystagmus, hypotonia, tremor, staggering and deviation in walking are frequently noted. Examples of such instances have been reported by Young,³⁴ Bramwell,³ Oppenheim,^{17a} Spiller,²⁴ Rhein²⁰ and others. Wakeley and Allen²⁷ stated that cerebellar signs which are not absolutely definite and develop with or after the appearance of general symptoms of increased intracranial pressure are false localizing signs and as such are of no value whatever in determining the site of the lesion.

In our experience there are other false localizing signs which occurred in the presence of tumors of the cerebellum with secondary hydrocephalus which deserve emphasis. The rôle that increased intracranial pressure plays in the production of these signs, we believe, is dominant. Evidence on this point is shown in the occurrence of convulsions and visual field defects which are discussed in detail.

Convulsions. The tonic "cerebellar fit" has been recognized as the characteristic convulsive pattern frequently present in patients with tumor of the cerebellum. Description of this type of convulsion was made by Wurfibain³³ in 1691 and later defined by Jackson.^{14a}

Attention has been given mainly to the tonic convulsion although it has been recognized that other patterns occur. This fact is mentioned by Jackson himself who quoted case reports of clonic convulsive movements in patients with tumor of the cerebellum and by Oppenheim,^{17b} Stewart,²⁵ Collier⁴ and others. Collier in particular emphasized the occurrence of clonic as well as tonic convulsions as a false localizing sign in cases of tumor of the cerebellum when increased intracranial pressure was established.

A consideration of the findings here reported showed that a variety of types of convulsions occurred. These ranged from synopal attacks located at one end of the "convulsive spectrum" to tonic fits at the other. Attention in the literature has been given mainly to the tonic cerebellar fit and a number of explanations have been offered to account for it. It is logical, however, that if other varieties of convulsive seizures occur, they too demand an explanation. Furthermore, it is reasonable to suspect that a common mechanism accounts for the various convulsive manifestations.

A review of the literature on this subject was recently made and reported.²⁸ A conclusion arrived at was that both the tonic cerebellar fit and the other types of convulsive phenomena were expressions of temporary cerebral anemia. This explanation was based upon the experimental work of Cushing,^{5c} Eyster, Burrows and Essick,⁹ and Wolff and Forbes,³² all of whom showed that sudden increases of intracranial pressure produced convulsions. The convulsions were the result of the temporary cerebral anemia caused by elevating the intracranial pressure above the systolic blood pressure. The same chain of events may follow when a patient with increased intracranial pressure suddenly increases the pressure by straining at stool, vomiting, struggling, and so on. The tonic cerebellar fit was therefore described as a *decortication phenomenon* not as a *decerebration phenomenon* for it does not seem likely that cerebellar tumors can cause a physiologic transection of the brain stem. Tonic fits may be seen in a variety of pathologic conditions which have in common physiologic or pathologic decortication.

It was also pointed out that ischemia of the brain may manifest itself initially by exaltation of function accounting for the occasional presence of convulsions of the cortical excitatory type. On the other hand, syncope may be the first and the mildest expression of transient cortical ischemia.

In brief, there is sufficient physiologic information at hand to account for the occurrence of various types of convulsions with tumors of the cerebellum on the basis of alterations in cerebral blood-flow. These alterations in bloodflow can be occasioned by transient changes in the relationship of the intracranial pressure to the systolic blood pressure.

Visual Field Defects. For the purposes of focal neurologic diagnosis, it is generally accepted that visual field defects indicate direct

involvement of the visual pathways at some point. This is thought to be so reliable that often intracranial operations are planned and performed solely on the information obtained from examination of the visual fields.

In the material reviewed, visual field defects resulting from the effects of distant lesions upon the visual pathways were noted in 8 cases. In most instances they appeared so significant to the examiners that the diagnoses were confused and it became necessary to rely upon pneumographic studies to establish the correct site of the tumors.

Although visual defects are an unusual finding in cases of tumor of the cerebellum, a number of cases have been reported. Gowers¹¹ was aware of their occurrence; Oppenheim^{17c} mentioned that he had seen the middle portion of the optic chiasm so compressed by a bulging third ventricle that in 1 case "only two thin threadlike processes showed the course of the optic nerves." The latter stated that cerebellar tumors may produce ventricular distention and so be the cause of a bitemporal hemianopsia. Wohlwill³¹ also stated that in hydrocephalus, the protruding third ventricle may compress the chiasm against the sella and produce bitemporal hemianopsia or simple optic atrophy. Cushing cited a case of distended third ventricle resulting from a blocked cerebral aqueduct which produced a combination of optic atrophy and bitemporal hemianopsia. Cushing and Walker,⁷ in an early paper, discussed the occurrence of binasal hemianopsia associated with cerebellar tumors.

Theoretically at least, since internal hydrocephalus and a distended third ventricle eventually accompany all cases of cerebellar tumors, evidences of chiasmal compression should not be unusual. This is apparently not the case. In many instances the hydrocephalus is minimal and the patient is operated upon before late symptoms occur. The anatomic relationship between the third ventricle and the chiasm is a second factor. As Schaeffer²³ showed in his fundamental anatomic researches on the optic chiasm, this structure is not always in the same position. In only 12% of the bodies examined was the relationship exactly as depicted in standard anatomies. Thus, variations in the position of the chiasm allow many different anatomic relationships with the downwardly distending third ventricle.

De Schweinitz,⁸ in the Bowman Lecture, devoted a section to anomalies of the arteries comprising the Circle of Willis. He described how indentations of the optic nerves and chiasm could be produced by these vessels if, as frequently occurs, the chiasm were dislocated. He showed how the posterior communicating artery, as it runs beneath the optic tract, could produce an homonymous hemianopsia if the distended third ventricle pushed the optic nerve against the vessel.

In the group of patients with visual field defects here reported, a

marked distention of the third ventricle was found in every case in which ventricular studies were performed or where necropsy was permitted. It is reasonable to believe that the distended third ventricle may have produced the defects found. As a corollary point, the presence of a visual field defect in a case with increased intracranial pressure does not exclude the presence of a tumor of the cerebellum.

Other Ophthalmologic Findings. Papilledema was reported as absent in 15 cases in which a tumor of the cerebellum was later found. It is recognized that this absence is not unusual in the presence of widened cranial sutures. Twelve of the cases, however, were beyond 20 years of age. In a number of instances, absence of this finding confused the diagnosis.

Jackson^{14b} in 1881 reported upon the absence of choked disk in 3 patients, 2 of whom had lesions of the cerebellum. van Wagenen²⁶ reviewed 1 year's series of cases from Cushing's clinic and found that of 45 subtentorial tumor cases, 6 showed no papilledema. Three of these were cases of cerebello-pontine angle tumors. Cushing and Bordley,⁶ in a clinical and experimental investigation of the subject, stated that they believed that the tendency of disks to develop papilledema varied greatly, thus accounting for variations in the presence of increased intracranial pressure. The literature indicates that the finding of papilledema in patients with a tumor in the posterior fossa is apparently higher than in cases with supratentorial lesions. Paton¹⁸ and Brain¹ found normal fundi in approximately 20% of cases with supratentorial tumors. Others have reported an even higher percentage. The strategic position of the posterior fossa tumors would seem to account for the difference. The fact remains, however, that papilledema may be absent in the patient with a tumor of the posterior fossa although elevation of the intracranial pressure exists.

The incidence of failing visual acuity was high in patients with tumors of the cerebellum. Eleven cases were totally blind at the time of admission to the hospital while 3 were blind in one eye. Cushing^{5b} reported a similar high incidence of visual loss. Of 61 cases of medullo-blastomata, 26 were reported to have impaired sight at the time of admission and 9 were blind. Cushing^{5a} pointed out that the "symptomatic onset (of a case of tumor of the cerebellum) may relate to vision alone." This observation has been confirmed.

Transient attacks of blindness occurred in 5 patients and was of late occurrence in the course of the patient's disease lasting from a few minutes to several hours. De Schweinitz⁸ stated that periods of temporary amaurosis may occur as part of the ocular symptomatology of hypophyseal tumor exactly as they do in ordinary brain neoplasms. "They depend upon pressure on the chiasma from the third ventricle." The fact that such attacks were observed to occur

only late appears to support De Schweinitz's observation. Cushing,^{5a} however, reported a case in which the onset of the patient's illness was marked by periods of fleeting blindness. An alternate explanation may be transient disturbances in central bloodflow—the blindness expressing the disturbance in the occipital lobes.

The occurrence of visual hallucinations in cases of tumor of the cerebellum is an interesting finding. There were 8 such instances concerning which the information appeared to be reliable. The localizing importance of this finding has been emphasized in neuroophthalmologic literature, and modern textbooks of neurology suggest that it is possible to differentiate a lesion of the temporal pole from that of the occipital on the basis of the type of visual hallucination experienced. Brain and Strauss,² Wechsler,²⁹ Grinker¹² and Purves-Stewart¹⁹ in their textbooks stated that visual experiences associated with lesions of the occipital lobe are confined to flashes of light and color and other so-called simple phenomena, while complex and elaborate images are found associated with lesions of the temporal lobe. According to these concepts, it would appear that visual hallucinations due to other lesions are unusual. Their occurrence in patients with tumors of the cerebellum, therefore constitute false localizing signs. Weinberger and Grant,³⁰ in a review of the subject of hallucinations associated with brain tumors, pointed out that the current conceptions of the localizing value of hallucinations may not be in keeping with the facts. The concept that certain areas of the cortex are so highly organized psychically as to produce visual hallucinations on stimulation by a tumor is neither sound physiologically nor psychologically. Visual hallucinations are highly integrated and complicated psychologic phenomena and require the activity of the entire brain. They may be excited, as these writers have shown, from any level of the neuro-optical apparatus. In their analysis of the published cases of hallucinations accompanying brain tumors, they pointed out that no localizing significance can be attached to the complexity of the images seen; that the hallucinations do not necessarily appear in the hemianoptic field and that tumors invading only the optic nerves may yield hallucinations indistinguishable from those reported in occipital or temporal lobe tumors. The hallucinations that occurred in patients with tumors of the cerebellum add further evidence to support that conclusion. It would be reasonable to suspect the dilatation of the third ventricle with compression of the optic chiasm as the cause of the phenomenon.

In the material reviewed, there were 41 cases in which nystagmus was absent and 18 which showed vertical nystagmus. Holmes¹³ stated that very few lesions of the cerebellum fail to show nystagmus in some form or other. This finding, he reported, was absent in 3 cases of gunshot injuries that he studied but it occurred in all of his cases of cerebellar tumors. The presence of this finding, we

have noted, focuses attention to the cerebellum immediately; when absent, however, doubt as to posterior fossa localization was raised in a number of cases. Nystagmus is apparently considered to be an important criterion of cerebellar disease.

Cushing^{5a} pointed out in a review of cases of astrocytoma of the cerebellum that "nystagmus is often wholly absent or represented by merely a few fine, poorly sustained twitches." Keschner and Grossman¹⁵ reported horizontal nystagmus as present in 23 of 29 cases of intracerebellar tumors. In 9 instances, the nystagmus was also vertical in direction. These authors further stated that they did not find any correlation between the degree of intracranial pressure or the degree of asynergia and nystagmus. We were able to confirm this statement.

Vertical nystagmus was noted by Holmes¹³ to "occur more commonly when the vermis was involved though it may be seen when the injury is limited to one half of the cerebellum." Of 18 instances of vertical nystagmus which were observed in our series, 12 patients had lesions involving the vermis. Fisher and Glaser¹⁰ have emphasized the point that the presence of vertical nystagmus is pathognomonic of intrinsic brain disease since the phenomenon is never produced by a peripheral lesion.

Lumbar Puncture. It is interesting that lumbar punctures were performed without untoward results in 50 cases with tumors of the cerebellum. In 11, the pressure was normal. In 4 of the latter group, papilledema was absent, thus serving to confuse the diagnosis. A number of observers commenting on this finding felt that the absence of increased intracranial pressure, as indicated by the intraspinal pressure, ruled out the presence of a posterior fossa tumor. Although Cushing^{5c} suggested that lumbar puncture was "hazardous as it may tend to a sudden wedging of the bulb," others have not found it so. Masson^{16a} reported 32 cases of tumor in or around the cerebellum in which serious symptoms did not follow the withdrawal of a small amount of fluid by lumbar puncture. Earlier recognition of cases with tumor of the cerebellum may account for hospitalization before clinical evidence of increased intracranial pressure occurs. Thus a tumor of the cerebellum apparently cannot be ruled out on the basis of either a normal spinal fluid pressure or absent papilledema.

Roentgenographic Studies. Survey Roentgen examination aided in diagnosis by showing signs of increased intracranial pressure in one-third of the cases examined. Indirect localizing signs of tumor other than well-known evidences of increased intracranial pressure were wanting except in a few instances. Rossier²¹ has reported a characteristic deformity of the basilar plate in 14 of 28 cases of cerebellar tumor, an interesting finding upon which our material does not permit comment. Masson^{16b} reported an incidence of 12% of calcification in 25 cases of medullo-blastomata and 20% in

29 cases of astrocytoma. Although we have found a low incidence of calcification, this finding may be an aid to diagnosis as Roentgen technique and apparatus improve.

There was ventriculographic evidence of a posterior fossa tumor in 21 of 37 instances in which the procedure was performed, a procedure reserved for cases of obscure diagnosis. In 12 cases, the Roentgen evidence suggested supratentorial lesion. Ventricular estimation employed in place of ventriculography was a source of error in 3 of the total of 5 incorrect final diagnoses resulting in supratentorial explorations.

Sensory Phenomena. Subjective sensory complaints were not unusual and have been occasionally reported by others. Sargent and Greenfield,²² in the case of a cyst of the cerebellum, reported that the patient had attacks of a tingling sensation in the left arm extending to the face. Similar types of sensory attacks were present in 11 members of our group of cases. Loss and diminution of corneal sensation were also observed. It would appear possible that sensory phenomena occur probably as a result of increased intracranial pressure as pointed out by Collier.⁴

Caloric Examination. Caloric examinations which were carried out in 41 patients of this series were misleading in 5, suggesting a lesion above the tentorium, and normal in 9. Various results have been reported as to the efficiency of this diagnostic procedure which appears to depend upon the astuteness of the examiner. Fisher and Glaser¹⁰ reported excellent localizing results. Of 25 cases, only 3 were not localized to the side of the lesion and but 1 was wrongly placed. On the other hand, Keesner and Grossman¹⁵ stated that in 29 cases, the "results of the tests were in full accord with the neurologic results in 6 cases." They believe that the caloric tests are considerably more valuable and reliable in localizing cerebello-pontine angle tumors than intracerebellar lesions, a conclusion which we support.

Tendon Reflexes. In our records, tendon reflexes showed a remarkable variation, a feature of cerebellar disease which has been noted by others.^{5b 15,27} Holmes¹³ emphasized the significance of the pendulous tendon reflex. This was infrequently observed in the patients of this series. Our findings correspond to those of Cushing's who noted dampening of the deep reflexes until the intracranial pressure increased with internal hydrocephalus and there was direct compression of the brain stem involving the pyramidal tract. We believe with others that in cases of tumor of the cerebellum, the reflexes have little localizing value.

Cranial nerve palsies were frequent and, in a number of instances, confused the diagnosis. A paralysis of the third nerve was observed in 11 cases. The syndrome of the cerebello-pontine angle was clear-cut in 4 cases. Complete or incomplete involvement of the third,

fourth, fifth, sixth, seventh and eighth cranial nerves was frequent. Holmes¹³ stated that true ocular palsies never result from lesions limited to the cerebellum. Thus, again there is evidence to show the rôle of increased intracranial pressure in producing false signs leading to error in diagnosis or management.

Summary. A review has been made of 158 cases of tumor of the cerebellum from the standpoint of unusual symptomatology and findings. The analysis was undertaken in order to clarify the obscure type of case by an understanding of false localizing signs which occur with increased intracranial pressure.

Attention was directed to the occurrence of convulsions and visual field defects which were found to occur in patients with tumor of the cerebellum.

Ophthalmologic findings, spinal fluid pressure, Roentgen findings, sensation, caloric examination results, cranial nerve involvement and tendon reflexes were briefly discussed.

The usual findings in cases of cerebellar tumor were charted.

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CEREBROSPINAL FLUID PROTEIN VALUES DETERMINED BY TYROSINE EQUIVALENT METHOD.

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THE determination of spinal fluid proteins has not kept abreast with the accuracy generally achieved in clinical chemistry. The old method of adding a protein precipitant to the spinal fluid and comparing the resulting cloudiness with turbidity standards has long been recognized as grossly inaccurate. Recently these errors have been subjected to analysis.³ At best, even the values found to fall in the lowest ranges have been only poor guesses. Protein values for pathologic fluids obtained by mere comparison of turbidity are always subject to uncertainty. Varying concentrations of other constituents affect the quality of the precipitate, therefore, the light absorption, transmission, reflection and dispersion.

Several investigators using the Dennis-Ayer method have claimed that the use of a colorimeter appreciably reduces the errors of this turbidity method. A claim of agreement within 12 mg. per 100 cc. between this method and Kjeldahl methods has been made.¹ This still leaves a high percentage of error when it is considered that often the total protein value is not twice that figure. The work of Merritt and Fremont-Smith,⁴ undoubtedly the most comprehensive in the literature, outlines in detail a modification of the Dennis-Ayer method; and the conclusions listed are based mainly on determinations performed by that method. At about the time this monograph appeared, Johnston and Gibson² published a procedure which is highly accurate and practical for the determination of spinal fluid protein. These workers modified the method which employs the Folin-Ciocalteu phenol reagent to determine the tyrosine equivalent of the protein present, and in their publication gave a graph showing the distribution of 500 spinal fluid protein values done routinely for the Department of Neurology.

When we began using the Johnston and Gibson modification in this laboratory we were asked to give the normal range for the method. In the course of determination of this range we also collected data on many pathologic fluids. There is an absence in the literature of data on either the normal or pathologic values for cerebrospinal fluid proteins by this method. We, therefore, present our findings in both instances.

Method and Material.—The method used for determination of spinal fluid protein was that described by Johnston and Gibson.² All fluids were drawn and stored under sterile conditions. Analyses were performed on the fresh specimens, with the exception of about 150 samples which were aged

about 2 days. This period of aging for sterile fluids was proved to have no effect on the protein value. Specimens were obtained by lumbar puncture. Some fluids from patients with cord tumors came from different levels. About 250 analyses were performed by the Department of Pathological Chemistry, State University of Iowa, on fluids from the University Hospital. Of the specimens analyzed in our laboratory 200 were furnished by Dr. L. P. Ristine, Mt. Pleasant State Hospital; the remainder were obtained from private patients in the Iowa Lutheran Hospital. Diagnosis in all cases represents concurrence of opinion of two or more staff members at these institutions. When a diagnosis of more than one pathologic condition was made, the condition probably having the greatest effect on the protein was selected for classification.

Discussion. The findings on spinal fluids from 100 persons diagnosed as normal are summarized in Table 1.

TABLE 1.—SPINAL FLUID PROTEIN VALUES FOR NORMAL PERSONS.

Diagnosis: Normal.

Age: Eight months to 72 years.

Number of cases: 100 (male and female).

Spinal fluid protein: Average, 31.6 mg. per 100 cc. Range, 15.4 to 46 mg. per 100 cc.

Distribution:

6% of the cases had a protein concentration less than 20 mg. per 100 cc.

37% had 20 to 29.9 mg. per 100 cc.

37% had 30 to 39.9 mg. per 100 cc.

20% had greater than 40 mg. per 100 cc.

The occurrence of three values between 45.0 mg. per 100 cc. and 46.0 mg. per 100 cc. pretty well fixes the upper limit of normal for this series at 46.0 mg. per 100 cc. Because of the wide margin of error in preëxisting methods, values heretofore were usually given in multiples of five.

A scatter diagram was made for spinal fluid values against the ages of the subjects. The only order recognizable in this table was the occurrence of ages under 1 year in the region of protein concentrations less than 20 mg. per 100 cc. Concentrations in fluids from persons over 60 years of age had a tendency to be high. The three highest normal values, however, were from persons 30 to 40 years of age.

The protein values which may be expected in pathologic conditions are indicated in Table 2.

In many instances it may appear that there are not sufficient cases to draw valid conclusions about the range or average value. Nevertheless, the conclusions indicated by these cases coincide sufficiently well with the extensive work of Merritt and Fremont-Smith¹ to warrant the publication without further accumulation of data.

To determine what relation the normal average protein value of 31.6 mg. per 100 cc. for both sexes bore to the average for each sex the figures were averaged separately. Seventy per cent of the 100 cases were males with an average protein value of 32.6 mg. per 100 cc; 30% females with a corresponding value of 27.5 mg. per 100 cc.

That body dehydration has little effect on spinal fluid protein concentration is shown in Table 3.

TABLE 2.—SPINAL FLUID PROTEIN VALUES IN VARIOUS PATHOLOGIC CONDITIONS.

Diagnosis.	No. of cases.	Protein concentration.		No. of cases above 46 mg. per 100 cc.
		Average (mg. per 100 cc.).	Range (mg. per 100 cc.).	
<i>Organic psychoses with:</i>				
Senility	14	49.9	23.6-203.0	4
Alzheimer's disease (autopsy)	2	53.9	44.5-63.4	
Cerebral arteriosclerosis	17	37.9	23.0-64.8	4
Neurolues (all types)	40	56.8	11.0-156.0	21
Brain tumor	20	119.3	14.0-540.0	
Brain abscess	3	492.0	51.0-877.0	
Cerebral embolism	16	47.6	24.0-91.0	6
Cord tumor	10	139.1	14.0-538.0	
Syringomyelia	2	128.0	57.0-199.0	
Paralysis agitans	2	24.5	24.0-25.0	
Multiple sclerosis	20	39.8	17.0-77.0	5
Meningitis	9	258.7	19.0-912.0	
Myelitis	7	78.6	27.0-216.0	
Encephalomyelitis	8	148.0	26.0-272.0	
Poliomyelitis	3	80.0	37.5-163.0	
Infectious polyneuritis	3	57.4	52.0-63.3	
<i>Encephalitis:</i>				
Traumatic	2	40.0	36.0-44.0	
Epidemic	2	53.0	49.0-57.0	
Chronic	14	47.2	16.0-221.0	3
Chronic alcoholism	4	57.9	47.5-75.0	
Acute alcoholism	7	40.1	27.7-48.8	
Drug addiction	3	39.5	26.0-47.2	
Neuritis and alcoholic neuritis	17	56.7	22.0-122.0	8
Neuralgia	10	35.5	28.0-52.0	1
Migraine	3	25.0	24.0-26.0	
Hypertension	5	32.8	24.0-37.0	
Pernicious anemia	3	36.3	35.0-39.0	
Miscellaneous organic diseases	5	42.2	28.5-55.0	
<i>Functional psychoses:</i>				
Manic depressive (all types)	17	33.0	17.0-71.0	3
Involuntary melancholia	11	38.9	24.1-47.0	2
Dementia præcox	28	34.7	21.0-57.0	6
Epileptic	18	36.8	23.0-64.0	3
Paranoia and paranoid condition	26	31.1	17.0-57.0	1
Psychoneurosis and neurosis	27	30.0	18.0-41.0	
Mental deficiency	10	42.0	20.0-114.0	4
<i>Without psychoses:</i>				
Chronic alcoholism	32	34.3	19.0-45.7	
Mental deficiency	8	35.4	23.0-48.0	1
Psychopathic personality	4	36.2	28.0-41.0	
Cardiac and gall bladder disease	5	32.6	16.0-42.0	
Arthritis of spine	6	45.0	31.0-60.0	
No neurol. diagnosis (uremia)	7	55.9	47.0-70.0	

TABLE 3.—SPINAL FLUID PROTEIN VALUES IN CASES OF DEHYDRATION.

State of dehydration.	Cases.	Protein concentration.	
		Average (mg. per 100 cc.).	Range (mg. per 100 cc.).
Moderate	14	34.9	27.7-45.2
Extreme	7	35.6	22.8-45.2

These figures are drawn from cases of psychosis, epilepsy, paranoia, and neurosis having protein values lower than 46.0 gm. per 100 cc. Cases with values above this are worthless for drawing a conclusion in this instance.

Summary. 1. Total proteins have been determined by the tyrosine equivalent method on 550 cerebrospinal fluids taken from persons in health and disease.

2. The upper limit of normal values has been found to be 46.0 mg. per 100 cc. The ranges for pathologic values agree well with generally accepted figures in the literature.

3. The average protein values for females is less than that for males.

4. Dehydration does not appreciably affect the protein concentration.

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NOTE ON A CRETIN'S RESPONSE TO TYPHOID INOCULATION.

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THE relation of the endocrine glands to the mechanism and manifestations of the immune state has been discussed for a great many years. In an early book on the endocrines, Bandler¹ (1921) stated that, "The maintenance of the normal state in the various structures of the body is vested in the ductless glands, and immunity, or lack of immunity to various diseases is more than probably one of the most direct evidences of their important function." Mills,¹⁶ in showing the effect of external temperatures on resistance, recently stated that, "Resistance to infection is closely dependent on body combustion level and ease of body heat loss," factors controlled in part by the endocrines. Cannon⁷ cites references to hormones as one of the non-specific mechanisms of defense.

Experimental studies have been mainly concerned with the extirpation of specific glands, followed by a study of the immune response of the animals subjected to such procedures. Lamoy and

Lévy-Bruhl¹⁵ surveyed the literature to 1915 and saw clearly the confusion, which exists to this day, in experimental work on this subject. For example, they report the work of Fassin and Marbé, who observed a decrease in the immune reaction in thyroidectomized animals, of Lerda and Diez who observed exactly the opposite effect, and of Fjeldstad, who noted no differences in his series of test animals. Launoy and Lévy-Bruhl¹⁵ removed the thyroid (and also the spleen) from chickens and noted no interference with the development of *Spirochaeta gallinarum* infections, indicating no increase in immunity. Garibaldi¹² found that the natural heterohemolytic power of the serum of thyroparathyroidectomized dogs is higher than that of normals. Houssay and Sordelli¹⁴ obtained conflicting results following the removal of the thyroid from different animals. They observed a weaker antibody response in the rabbit and horse and an increase in the antibody response of the dog. Parhon and Ballif¹⁷ noted that the removal of the thyroid had an attenuating action on anaphylactic shock in guinea pigs and permitted the animals to survive. This may be taken to indicate a decrease in immune response, rather than an increase. Stschedrowitzky and coworkers¹⁹ noted that the production of antibodies in thyroidectomized animals is considerably weaker after the operation and remained so when tested 6 months later. Haber,¹³ in studying the receptivity of rabbits to viruses, noted that thyroidectomy had no effect upon the time of development of encephalitis following infection with herpes virus. M. and A. Derevici⁹ noted increased immune reactions following removal of the thyroid from rabbits. The extirpation of the thyroid enhanced the activity of the spleen and is the possible explanation, say these authors, for the increased activity of the immune reactions. They reiterated that thyroid activity is antagonistic to splenic activity. Eickhoff and coworkers¹⁰ found the Arthus phenomenon to be inhibited in sensitized rabbits, following thyroidectomy. Artificial stimulation with thyroid hormone increased the reactions of rabbits in anaphylactic shock. Cope and Kapnick⁸ showed that the complement content decreased in the blood of thyroidectomized rabbits, while the response to vaccinia virus of the rabbit is not altered by the operation or by injected thyroxin. In addition, they noted that alterations in complement concentration are not related to the cevitic acid level in the blood.

The relationship of thyroid function to immunity in the human has not been discussed extensively. For a number of years, we have been interested (from a clinical point of view) in the incidence of various infections in our thyroid-deficient children before and after therapy. No definite conclusions have been drawn. We were able to study a 22-year-old cretin, who had not been treated with thyroid and who was available for immunologic experiments.

Case Report. F. D., a 22-year-old white male, a typical sporadic cretin, entered our institution on March 22, 1940, and remained 134 days, until

August 1, 1940. He was a full term infant, second born of a normal 9-month pregnancy, with 1 hour labor. The father is Polish, the mother American born, but of Polish descent. There are 6 other living children, 4 sisters and 2 brothers. The girls and the 8-year-old brother are well at present, but the 13-year-old boy is also a classical hypothyroid. (Familial sporadic thyroid deficiency is a rarity in this country.) When the boy reached the age of 3 years, the mother sought medical advice, because he did not grow and develop like the first child; his skin was very dry, the tongue was large, as were also the head and abdomen. The parent stated that the child stayed in the hospital for 1 year, at the end of which time he sat, walked and ate by himself, all of which he could not do before. From the age of 4 until the present time, the boy's condition was neglected.

Upon entrance, F. D. weighed 46 pounds and was 38½ inches tall, the development being about that of a 7- to 9-year-old. He spoke only in monosyllables,¹⁸ carried out a few simple commands, and had an intelligence quotient of a 3-year-old child.^{4,6} The dwarfed stature and mental inadequacy, in addition to supraclavicular fat pads, macroglossia,⁵ large abdomen and dry skin readily identified him.

Roentgenograms of the bones revealed marked retardation of skeletal growth, with fragmentation and stippling of the epiphyses of the humeri and femori. The ossification at the wrist corresponded to that of a 6-year-old. Mixed dentition of the permanent and deciduous teeth was present.¹¹ The films of the heart revealed a cardiac enlargement which was also found on percussion and the electrocardiograph showed low voltage in all levels.³ The systolic blood pressure was 118 and the diastolic 80.

The initial blood cholesterol was 534 and then fell to normal upon administration of thyroid extract.^{2,a,b} Basal metabolic determinations were impossible because of lack of coöperation. Urine and spinal fluid chemical examinations were entirely negative. The Schick and Dick tests were negative upon entrance.

Complete blood count: Hemoglobin, 11.5 gm.; erythrocyte count, 4,250,000; white blood cell count, 6200; myeloid-erythroid ratio, 6%.

Differentials: Neutrophils, 48%; lymphocytes, 30%; stab cells, 13%; mononuclears, 13%.

Blood Kahn and Wassermann tests and spinal fluid Wassermann tests were negative.

Cevitamic acid determination, 1.75 mg. per 100 cc. blood.

Liver function test: Intravenous bromsulphalein, 40% dye in 5 minutes; 0% dye in 30 minutes.

	At entrance.	After thyroid therapy.
Blood serum calcium	8 76	9 1
Blood serum phosphorus	4.62	4 4
Blood serum phosphatase	2 50	6.9

Experimental Study. We studied the patient's response to typhoid vaccine. An agglutination test performed April 20 was negative. The patient received 0.5 cc. of stock typhoid vaccine April 23, and 0.75 cc. April 30. An agglutination test was performed May 2 and was negative. The patient received 1 cc. of stock typhoid vaccine May 7. Agglutination tests performed May 9 and May 13 were negative. The test was again negative on June 20, when thyroid extract therapy was started, ½ grain daily. The dose was increased June 28 to 1 grain daily. An agglutination test performed that day showed partial agglutination. 1 to 80 dilution. The clumps were readily dispersed. The dose of thyroid extract was increased to 2 grains daily and was maintained after

the patient left the hospital. He has been seen regularly since that time and has greatly improved physically. On February 1, 1941, an agglutination test showed a strong positive titer of 1 to 80. The clumps could not be dispersed.

The phagocytic activity of the patient's cells for staphylococci and streptococci were studied and were found to be identical with the normal controls. No attempt was made to immunize the patient to these organisms. No change in phagocytic activity was found after the administration of thyroid extract. Normal adults before and after prolonged administration of thyroid extract showed no variations in phagocytic activity.

Conclusion. It appears that the patient showed no response to typhoid inoculation in the absence of thyroid activity. Following the administration of thyroid extract, antibody response was noted. This would seem to indicate a relationship between thyroid function and immune response.

Further studies of this relationship are indicated.

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MODIFICATION OF RESISTANCE TO ANOXIA, WITH ESPECIAL REFERENCE TO HIGH ALTITUDE FLYING.*

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A MARKED lowering of the pressure of oxygen in an organ of the body produces temporary impairment of function or permanent

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pathologic damage, depending on whether the tissue cell is sensitive to oxygen-want or relatively insensitive. Thus, complete stoppage of the oxygen supply to the lower limbs by compression of the arteries in the thigh has been maintained for over $1\frac{1}{2}$ hours without impairing the function of the muscles of the legs subsequently. On the other hand, asphyxia of the human brain for 5 minutes may result in intracranial hemorrhage or death. Guinea-pigs die in convulsions after inhaling 100% nitrogen for 50 seconds, which in itself is evidence of the special sensitivity of the brain to asphyxia.

The importance of mild degrees of anoxia in clinical and aviation medicine has been emphasized in the past decade. Patients with congestive heart failure and pulmonary emphysema, who at times show no cyanosis and only a slight lowering of the arterial oxygen saturation (88 to 93%), may be relieved of dyspnea and other symptoms of anoxia by inhalation of oxygen-enriched atmospheres. Local tissue anoxia may be severe in the presence of a normal arterial oxygen saturation, as in occlusion of the coronary and cerebral arteries; other clinical syndromes are being recognized in which oxygen treatment of cell anoxia is of value, such as shock and cardiac pain.

In studying the impairment of mental functioning at altitudes of 12,000 feet, we became impressed with the possible relation between "pilot error" and continuous anoxia at that altitude.² Recognition of the fact that emotional control and judgment are adversely affected by exposure to relatively mild degrees of oxygen-want is becoming general. On May 1, 1941, the Civil Aeronautics Board inserted the following amendment in its regulations: "61.743 OXYGEN APPARATUS AND ITS USE. No air carrier aircraft shall be operated in scheduled air transportation at an altitude exceeding 10,000 feet above sea level continuously for more than 30 minutes, or at an altitude exceeding 12,000 feet above sea level for any length of time, unless such aircraft is equipped with an effective oxygen apparatus and an adequate supply of oxygen available for the convenient use of the operating crew and proper use is made of such apparatus."

In the present world emergency, military flying has been conducted at altitudes so high that anoxia occurs, even with the inhalation of 100% oxygen. The effect of increasing altitude on the alveolar oxygen pressure even in the presence of 100% oxygen is illustrated in Chart 1. The uppermost rectangle schematically represents the proportions of water vapor, CO_2 and oxygen in the alveolar air at sea level. The blank white space contains nitrogen and the rare gases. The oxygen molecules are represented by 10 black circles, illustrating an alveolar oxygen pressure of 103 mm. Hg. The next rectangle shows the increased number of oxygen molecules in the lung at sea level when 100% oxygen is inhaled. The alveolar oxygen pressure under these circumstances is 673 mm. Hg. When

the atmospheric pressure is reduced one-half, which occurs at an altitude of 18,000 feet, the original volume of air in the lungs has been expanded to twice the volume present at atmospheric pressure. At 33,700 feet it will be observed that the same number of oxygen molecules is present in the space which represents the lung air as was present in the air breathed at sea level, namely 10 black circles, representing 103 mm. Hg alveolar oxygen pressure. However, at 42,200 feet the volume of air in the lungs has been expanded to six times that present at sea level and the 5 black circles in the lung space now indicate an alveolar oxygen pressure of approximately 50 mm. Hg. It will be observed that the sum of water vapor and carbon dioxide occupy a proportionately larger percentage of the lung space at this high altitude. The pressure of CO_2 in the lung air is altered by the degree of hyperventilation.

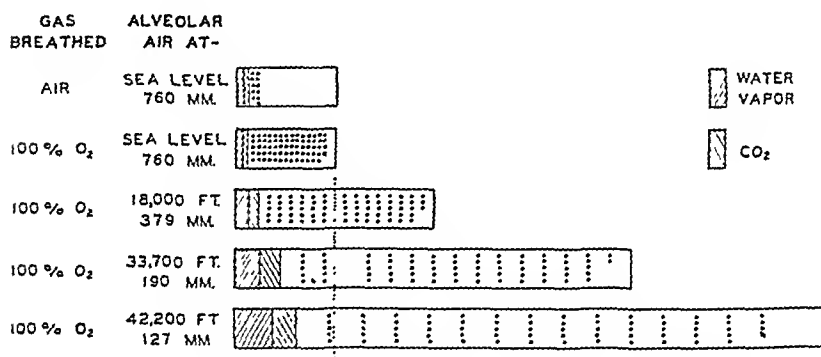


CHART I.—FALL IN ALVEOLAR OXYGEN PRESSURE WITH INCREASING ALTITUDE.

Since pressure cabins are not usually employed for altitudes of 40,000 feet, at which pilots have already flown during this war, it seemed of interest to study the circumstances which might increase or decrease the fitness of the individual in respect to resistance to acute oxygen-want. These factors may also play a rôle in certain disease conditions discussed above, in which latent or overt anoxia is present.

The first part of this paper illustrates a factor which aggravates the effects of anoxia, namely carbon monoxide poisoning as result of inhaling tobacco smoke. The second part deals with the increase in resistance to oxygen-want at high altitudes after total thyroidec-tomy.

The smoke from cigarettes yields approximately 1% carbon monoxide by volume, from pipe tobacco about 2%, and cigars about 6% carbon monoxide. Investigators have differed in their estimation of the importance of carbon monoxide poisoning as result of smoking; some consider it negligible whereas others believe that dangerous symptoms may result. Jones and his associates¹

have reported 5% CO in the blood of persons in a smoke-filled room, and Hartridge³ asserts that there may be 6% saturation in the blood of a moderate cigarette smoker. Since little or no absorption of carbon monoxide takes place from the mouth, the depth of inhaling and the length of time in which the inhaled puff is kept in the lungs are factors which cause variations in the results. We have made various investigations in 30 subjects but in this communication propose to summarize the results of 18 medical students who smoked 20 cigarettes from the time of arising to 3.30 P.M. when blood was drawn for the determination of carbon monoxide and the oxygen capacity. They were all individuals who considered themselves inhaling smokers and were specifically asked to inhale. The methods of analysis were those of Van Slyke.⁷

CHART 2.—EFFECT OF INHALING SMOKING OF 20 CIGARETTES.

Case No.	CO saturation arterial blood, per cent.	Remarks.
1	2.2	Lowest result
18	12.3	Highest result
Average (18 cases)	5.7	

The results are summarized in Chart 2 in which it will be seen that the lowest saturation of the blood with CO was 2.2% and the highest 12.3%, the average being 5.7%. Approximately one-half of the subjects tested had a carbon monoxide saturation of between 5 and 10% after smoking 20 cigarettes with inhaling. The effect of CO in displacing oxygen from the hemoglobin becomes less as the blood is subjected to a lower oxygen tension (Peters and Van Slyke).⁵ In an interesting study by Asmussen and Chiodi¹ it was shown that the ventilation and circulation are not stimulated by severe CO poisoning, as in hypoxemia due to breathing lowered oxygen concentrations, but that an acute lowering of the oxygen pressure in the tissues of the brain and heart and other organs takes place, at least partly due to failure of the compensatory stroke volume of the heart.

When a decreased saturation of the arterial blood with oxygen is present, such as at altitudes of 10,000 to 12,000 feet, when the pilot is not breathing oxygen, a saturation of hemoglobin between 6 and 10% with carbon monoxide will aggravate oxygen-want in the tissues. This would also be true at altitudes above 33,700 feet, even though the pilot was inhaling 100% oxygen, since anoxia is present under these conditions, as seen in Table 1. Further studies are in progress to determine to what extent the oxygen tension of the tissues will be lowered by carbon monoxide saturation of the hemoglobin between 6 and 10%.

The second factor to be presented in this paper is the effect of thyroidectomy on resistance to severe anoxia. In 1918 Strechli⁶ reported that thyroidectomized rats were less dyspneic and showed

fewer signs of collapse when exposed to low barometric pressures, as compared to normal animals. He further showed that splenectomy decreased the tolerance to anoxia and that it also nullified the beneficial effects of thyroidectomy.

TABLE 1.—SURVIVAL OF THYROIDECTOMIZED AND NORMAL RATS EXPOSED TO LOW BAROMETRIC PRESSURES FOR 2 HOURS.

Barometric pressure MM.	Equivalent altitude feet.	Normals.			Thyroidectomized.		
		Sur.	Died.	% mort.	Sur.	Died.	% mort.
226	30,000	5	0	0	5	0	0
206	32,000	9	1	10	5	0	0
187	34,000	6	4	40	5	0	0
170	36,000	1	10	91	5	0	0
155	38,000	0	5	100	6	0	0
141	40,000	0	5	100	5	1	17
128	42,000	0	5	100	4	1	20
111	44,000	0	5	100	3	1	25
105	46,000	0	5	100	0	3	100

We studied the effect of thyroidectomy on mortality in rats exposed to low barometric pressures, as well as to low oxygen concentrations. The accompanying table shows the mortality after a 2-hour exposure to various barometric pressures. It will be seen that the difference between the normal and the thyroidectomy group is indeed remarkable. Normal animals die at an altitude of 34,000 feet whereas the thyroidectomy group is alive up to an altitude of 42,000 feet. In chamber experiments about 75% of 30 thyroidectomized rats survived a 3-week exposure to 6% oxygen whereas 80% of a similar number of normal rats were dead within a period of 12 to 36 hours.

The importance of these observations will depend upon the extent to which they may be made applicable to flying conditions. It seems likely that pilots whose basal metabolism is 20% above normal would withstand very high altitudes less well than pilots whose basal metabolism is 20% below normal. Furthermore, measures may be found which will make possible a temporary lowering of the oxygen consumption. The physiologic explanation of these results in thyroidectomized animals would appear to lie in a higher oxygen tension in the tissues of the operated animals, as result of a far lower consumption of oxygen in the individual cells.

Conclusion. Carbon monoxide poisoning as a result of inhaling tobacco smoke may under certain circumstances become a factor which impairs resistance to anoxia, especially when the pilot is traveling without oxygen at altitudes of 10,000 to 12,000 feet, and also in the presence of 100% oxygen at altitudes between 34,000 and 40,000 feet. In 18 inhaling smokers, the average CO saturation of arterial blood was 5.7% after smoking 20 cigarettes from 9 A.M. to 4 P.M. Nine of the subjects had a carbon monoxide saturation between 5 and 10%.

Rats who have been thyroidectomized show a remarkable increase

in resistance to very high altitudes. Normal rats die at 34,000 feet in a 2-hour period, whereas thyroidectomized animals survive at barometric pressures which correspond to an elevation of 42,000 feet. The majority of thyroidectomized rats survive 3 weeks in a chamber kept at 6% oxygen whereas a similar percentage of normal rats die in 12 to 36 hours' exposure to this low oxygen concentration.

Additional studies are in progress to determine the significance of this degree of carbon monoxide poisoning as a result of inhaling tobacco smoke from cigarettes. The importance of variations in oxygen consumption is also being additionally studied in subjects exposed to low barometric pressures.

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STERNAL MARROW CHANGES DURING THE FIRST WEEK OF LIFE.

CORRELATION WITH PERIPHERAL BLOOD FINDINGS.

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THE sternal aspiration method of studying bone marrow is one which permits repeated examinations at short intervals of time. It was felt that this procedure might thus be used to advantage in an attempt to explain certain well-known hematologic changes which occur in the peripheral blood during the neonatal period.

At the time of birth, the blood of the normal infant* has a high content of red cells and hemoglobin and an elevated reticulocyte count, with a fall in red cells and hemoglobin soon after birth^{2,3,7,9-12,22,24,25,33,35,42,48,49a,50,51,53,55,59,65-67,75a,b,76-78}. The accepted explanation for these findings is that the change from low to high oxygen tension makes unnecessary in the newborn the large number of red cells which was required in the fetus.^{3,10,20,21,29a-c,30,34,35,37,44,47,52,67,77a,b,79} Thus, a breakdown of redundant red cells takes place.

* The infants studied were in the newborn nursery of the Jewish Maternity Hospital.

The destruction of these red cells is generally believed to be due to some marked hemolytic process occurring in the blood stream. However, this idea of excessive hemolysis might be questioned in view of the sharp drop in reticulocyte percentage during the first week of life.^{7,15,24,27,29a,b,39a,b,41a,51,63,76,78}

Along with the high red cell, hemoglobin, and reticulocyte levels at birth, there is also a high white cell count, which similarly has been attributed to hemopoietic hyperfunction caused by requirements of fetal existence.⁷ But how can one explain the leukocyte changes during the first week,^{6-9,12,14,26,39b,47,48,58,65,78} at which time the white cell count decreases and the blood picture at birth becomes one of lymphocytic predominance?

The present study was undertaken with the hope of advancing hematologic knowledge of the newborn period. By means of sternal puncture, we have sought to determine whether there was any correlation between the bone marrow picture and the peripheral blood, and whether the findings could point the way to a possible explanation for the changing blood picture in the neonatal period.

Since Arinkin's^{4a} introduction of the sternal aspiration method in 1927, there have been many reports of the sternal puncture findings in infants and children,^{16-19,23,28,31,40a,b,41b,43,46,60,64,72,74} but in only 3 of these has the method been described in detail. All used cut down lumbar puncture needles. Kato^{41b} used a needle 4 cm. long, and Diwany¹⁹ a needle cut short and fitted with a movable shield which could be fixed at any required distance; Vogel and Bassen⁷⁴ used an 18-gauge, $\frac{1}{2}$ -inch (1.27 cm.) needle, but mentioned that a 20-gauge, $\frac{1}{4}$ -inch (0.64 cm.) needle was preferable in infants under 1 year. The method to be reported here utilizes this $\frac{1}{4}$ -inch needle (Fig. 1). The procedure is simple and can be performed with safety and accuracy.

The Study. Blood counts and sternal marrow aspirations were done on 35 normal full-term infants (14 males, 21 females) in the first 24 hours of life and again 1 week later. The youngest was 2 hours old and the oldest was 23 hours at the time of the first examination.

Examination of peripheral blood, taken from the big toe, consisted of RBC count, hemoglobin determination, WBC count, differential, and reticulocyte count.*

The materials used in the sternal marrow aspiration were: 1, A dry sterile $\frac{1}{4}$ -inch, 20-gauge lumbar puncture needle. 2, A dry sterile 20-cc. glass syringe (Luer type). 3, Iodine and alcohol. 4, Sterile cotton balls and gauze pads. 5, White blood cell pipette. 6, White blood cell diluting fluid (2% acetic acid solution). 7, Clean glass slides.

* The diluent used in counting the RBC was Hayem's solution; 2% acetic acid solution was used in the WBC count (a correction was made for nucleated RBC). The Hb was determined by the method of Sahli (100% = 14.5 gm.).

The WBC differential was made by staining the spreads with Jenner and Giemsa stains and counting 100 cells.

The reticulocyte per cent was determined by counting 1000 erythrocytes in a spread stained by a 1% alcoholic solution of brilliant cresyl blue and then by Jenner and Giemsa stains.

The advantages of using a short needle are: 1, There is no fear of dangerous penetration into the chest cavity, for the hilt of the needle acts as a guard. 2, A small amount of material may be obtained without the possibility of admixture with peripheral blood. 3, Once the needle has penetrated into the marrow cavity it can be held firmly in position.

Technique. 1. The arms were immobilized at the sides and a pad was placed behind the shoulders in order to throw the head back. A nurse held the infant's head in this position.

2. The skin of the upper sternum was prepared with iodine and alcohol. No anesthesia was used.

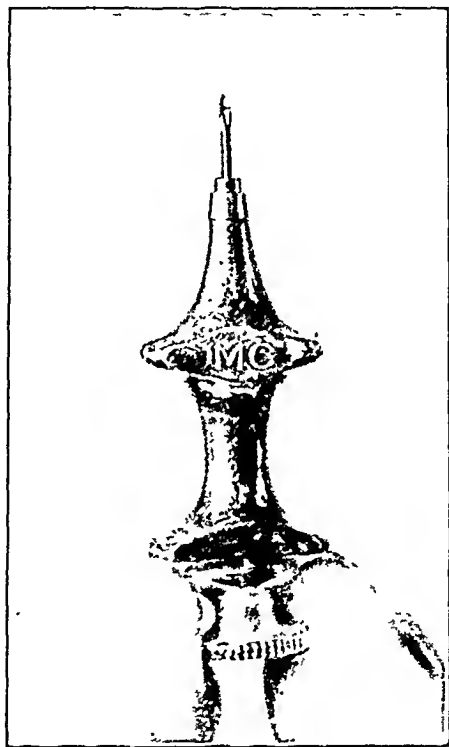


Fig. 1.—A 20-gauge lumbar puncture needle cut down to $\frac{1}{4}$ inch length.

3. The needle was inserted at the midline into the manubrium. This site was found to be best suited for puncture in infants because its slightly greater thickness permitted the needle to be well fixed in position. The needle was directed cephalad at an angle of about 45 degrees.*

4. The trocar was removed and the syringe was attached to the needle. Suction was applied until the marrow material appeared in the neck of the syringe. If at first no material was obtained the trocar was reinserted and the needle rotated *in situ*. If this also failed, as occasionally happened, the needle was withdrawn completely and reinserted in a nearby spot.

5. The needle and syringe were withdrawn and an alcohol sponge applied with gentle pressure to the puncture wound.

6. The contents of the syringe were expressed on a glass slide. From this a count was made of the nucleated cells, including the megakaryocytes, and smears were spread. These were stained with Jenner and Giemsa stains, 500 cells being counted in the differential.

* In infants and young children there is complete absence of the sudden give, so characteristic in the adolescent and adult when the needle penetrates through the hard outer bony shell into the marrow space.

TABLE 1—INDIVIDUAL PERIPHERAL BLOOD AND MARROW COUNTS IN FIRST 24 HOURS AND 1 WEEK LATER.

[illegible]

Classification of Bone Marrow Cells. The nucleated cells in the sternal marrow smears were identified according to the classification of Vogel and Bassen.⁷⁴ The cells noted were grouped under the following headings: Myeloblasts; Myelocytes; Eosinophilic myelocytes; Non-segmented neutrophils; Segmented neutrophils; Eosinophils; Basophils; Lymphocytes; Megakaryocytes; Hematogones; Reticulum cells; Nucleated RBC: Megaloblasts, Erythroblasts, Normoblasts.

Results. In Table 1 are given the data for the individual infants, arranged according to their age at the time of the first examination. The second line of figures under each number represents the findings 1 week later. Table 2 presents the average findings in the 35 infants studied.

Age. At the time of the first examination, the age of the infants varied from 2 to 23 hours (average, 11.4). There were no significant differences according to age in hours during the first day of life.

Sex. There were 21 females and 14 males. No important differences existed because of sex.

Weight. The weight averaged 7:2 (6:0-9:7) at time of the first examination and 7:5 (5:14-9:12) a week later. We found no relationship between birth weight and height of hemoglobin,^{49b} nor were any other noteworthy differences found because of weight.

Feeding. As may be noted in Table 1, most of the infants were breast fed, a few were on breast and formula, and a few were on formula exclusively. Consequently, no conclusions could be drawn from this factor. However, it does not seem likely that variations in adequate feeding should be of any consequence.

Jaundice. Although jaundice was present in no infant on the 1st or the 8th day, physiologic icterus occurred in 4 of the babies studied. This in nowise affected the hematologic picture.

Peripheral Blood. Hemoglobin. On the 1st day the Hb varied between 102-172%, averaging 135% (19.8 gm.). A week later it varied between 90-168%, and averaged 121% (17.6 gm.). In some cases, little if any change took place.

Red Blood Cells. On the first day the RBC varied between 4.23-7.15 million (average, 5.53 million). A week later the count dropped to a range of 3.40-6.14 million (average, 4.8 million). In some cases, little if any change took place. It may be noted that in most of these latter cases, moreover, the Hb change was also negligible.

White Blood Cells. On the 1st day the corrected WBC count varied from 12,100 to 43,250 (average, 24,000). A week later the count varied from 8350 to 27,650 (average, 14,200).

Differential. The myeloid cells dropped from an average of 70% down to 35% at the end of a week, with a shift to the right taking place. The lymphocytes increased from 25% to 59%. There was no significant change in the monocytes.

Reticulocytes. On the 1st day the reticulocytes varied between 1-4.7% (average, 2.3%); a week later the range was 0.1-1.2% (average, 0.4%).

Sternal Marrow. In a few cases not enough material was aspirated for a chamber count to be done, although spreads were made.

Nucleated Red and White Cells. The range was approximately the same on the 1st and 8th day, and although some infants showed an increased count after a week, the average decreased from 186,000 per c.mm. (54,000-358,000) to 134,000 (53,000-327,000). This difference did not seem to be of great importance.

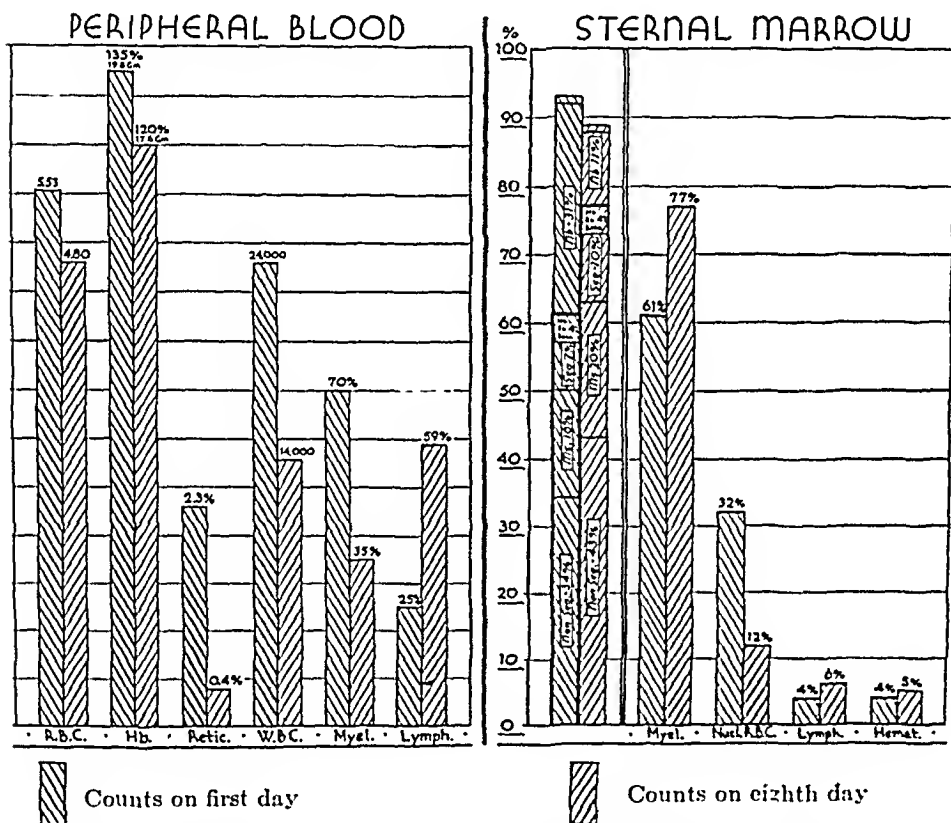


CHART 1.—Peripheral blood and sternal marrow findings on 1st and 8th day. The first two columns under sternal marrow show a comparison between the myeloid cells and the nucleated red cells on the 1st and 8th day. A heavy black line separated these two cell groups. It will be seen that the two groups comprise about 90% of marrow cells on both days. The figures of the 1st day total 101% because round figures were used.

Megakaryocytes. On the 1st day the figures varied between 0-264 per c.mm., whereas the range a week later was 0-220. No significant changes took place in this period of time.

Differential (Chart 1). The myeloid series and the nucleated red blood cells comprised about 90% of the nucleated cells both on the 1st and the 8th day; lymphocytes and hematogones made up most

of the rest. However, a striking change in relation was noted in every case after a week's time. On the first day of life the percentage of myeloid cells averaged 61% and the nucleated RBC 32% (16.4-49%). On the 8th day the myeloid percentage had increased to 77%, whereas the erythroid elements dropped sharply to 12% (5-23%). Thus, the Myeloid/Erythroid Ratio increased from 1.9 to 6.7. Presented in a slightly different fashion, there were about one-half as many nucleated RBC as myeloid cells on the 1st day but only one-seventh as many on the 8th day.

TABLE 2.—AVERAGE PERIPHERAL BLOOD AND MARROW COUNTS IN FIRST 24 HOURS AND 1 WEEK LATER.

	All cases.		Females		Males.	
	1st 24 hrs	Wk. later.	1st 24 hrs.	Wk. later.	1st 24 hrs.	Wk. later.
Age in hrs.	11 4		11 3		11 7	
Wt. (lbs. and oz.) . . .	7:02	7 05	7.00	7 03	7.12	7:13
<i>Peripheral blood chamber count:</i>						
Hb., %	135 1	120 6	131 6	117 1	140 4	125 7
Hb., gm. per 100 cc. . .	19 8	17 6	19 3	17 1	20 5	18 3
RBC (millions)	5 5	4 8	5 4	4 7	5 7	5 0
WBC (thousands) . . .	24 0	14 2	24 9	14 1	23 0	14 7
<i>Peripheral blood smear:</i>						
Myelocyte	0 8	0 0	0 9	0 1	0 8	0 0
Non-segmented	13 5	2 5	12 3	2 3	15 4	2 9
Segmented	54 6	31 5	54 5	29 0	54 6	35 1
Eosinophil	0 9	1 1	0 9	1 3	1 1	0 7
Basophil	0 3	0 2	0 4	0 2	0 2	0 1
Lymphocyte	24 9	58 6	26 4	60 6	22 7	55 6
Monocyte	5 0	6 1	4 7	6 5	5 2	5 5
N. per 100 WBC	1 2	0 1	1 2	0 1	1 2	0 0
Reticulocyte, % . . .	2 3	0 4	2 4	0 4	2 2	0 3
<i>Sternal marrow chamber count:</i>						
Nucleated RBC and WBC	185,843	134,200	190,375	103,526	180,714	171,583
Megakaryocytes . . .	58 7	82 9	74 3	62 3	40 9	105 3
<i>Sternal marrow smear.</i>						
Myeloblast	0 8	1 5	0 7	1 5	1 1	1 5
Myelocyte	16 3	19 7	17 0	18 1	15 9	22 1
Myelocyte Eo	0 6	0 6	0 6	0 6	0 6	0 5
Non-segmented	33 9	43 5	36 7	45 1	29 6	41 0
Segmented	7 0	10 4	6 8	10 4	7 2	10 5
Eosinophil	2 0	1 7	1 9	1 7	1 6	1 6
Basophil	0 0	0 0	0 0	0 0	0 0	0 0
Lymphocyte	3 8	6 2	3 4	6 7	4 2	5 5
Megakaryocyte	0 1	0 1	0 1	0 1	0 0	0 1
Hematogone	3 8	4 8	3 8	5 4	3 5	3 9
Reticulum	0 0	0 1	0 0	0 0	0 0	0 2
Megaloblast	0 1	0 1	0 1	0 1	0 1	0 0
Erythroblast	1 0	0 5	1 1	0 5	1 0	0 5
Normoblast	30 8	11 0	28 0	10 0	35 1	12 5
Total nucleated RBC . .	31.9	11 6	29 2	10 6	36 3	13 1
Myeloid/Erythroid ratio	1 9	6 7	2 2	7 3	1 5	5 9

Examination of the figures for the myeloid cells in Tables 1 and 2 revealed that with few exceptions the non-segmented neutrophils were the most abundant on the 1st day and that they showed the greatest increase at the end of the week. There was also an average increase in the myelocytes and segmented neutrophils.

The lymphocytes and the hematogones each represented about 4% of the nucleated bone marrow cells in the 1st day. The increase by the 8th day was slight.

Discussion. *Peripheral Blood.* Comparing our figures with those of others, we note that in general our findings in the peripheral blood agree with those of earlier investigators. Here it is important, not that figures reported by various authors have differed from one another, but that they have indicated the direction of the changes in the blood during the neonatal period.

Hemoglobin. It has been established that the high hemoglobin content of the blood diminishes within the first few weeks of life. Regardless of when the greatest drop takes place,^{13,22,24,32,42,66} our cases showed a fall from 135% (19.8 gm.) on the 1st day to 121% (17.6 gm.) a week later. Mackay's^{49a} figures in the same period of time fell from 19.7 to 17.9 gm., and Sanford's⁵⁷ fell from 18.8 to 15.6 gm.

Red Blood Cells. Our cases had an average count of 5.53 million on the 1st day. This coincides closely with the figures of Lucas⁴⁸ (5.51 million), Mitchell⁵³ (5.68 million), Faxen²⁴ (5.78 million), Sanford's⁵⁷ (5.8 million), and Slawik⁶⁵ (5.85 million). On the 8th day our cases averaged 4.8 million, Lucas'⁴⁸ averaged 4.5 million, Sanford's⁵⁷ averaged 5 million and Faxen's²⁴ averaged 5.12 million. Wollstein,⁷⁸ on the other hand, found the RBC count on the 7th day to be higher than at birth, falling below birth level early in the second week.

White Blood Cells. It is universally agreed that the high white cell count at birth falls during the first week of life, the figures varying with different investigators. On the 1st day we found 24,000, Bakwin and Morris⁸ reported 20,300, Lippman⁴⁷ found 22,500 at 12 hours, and Frank²⁶ found 29,000 at 12 hours. On the 8th day our cases averaged 14,200, Bakwin and Morris's⁸ 10,200, Frank's²⁶ 10,700.

Differential. Here too there is unanimity of opinion, namely, that the large number of myeloid cells at birth becomes reduced, with a shift to the right taking place at the end of the 1st week, at which time the picture also shows lymphocytic predominance. Our figures of 70% myeloid cells on the 1st day and 59% lymphocytes on the 8th day are almost identical with those summarized by Baar and Stransky.⁷

Reticulocytes. Of great significance is the drop in reticulocyte percentage which takes place during the 1st week of life. This finding is unquestioned. Our figures dropped from 2.3% in the first 24 hours to 0.4% on the 8th day. For the same period of time. Faxen²⁴ reported a fall from 2.2% to 0.38%, and Merritt and Davidson⁵¹ found a drop from 3.4% to 0.17%. Krummbhaar's⁴⁵ counts, starting at 4.5% 4 hours after birth, dropped to 1.7% at the end of 24 hours and were stabilized at 0.3% by the 10th day. Woll-

stein's⁷⁸ figures for the 1st day were 1.2-2.6%, falling below 0.5% by the 10th day.

Bone Marrow. Before attempting to compare our study with those of others who have carried on similar investigations in this age group, it would be wise at this point to summarize briefly the essential findings (Chart 1): In the 1st day of life the myeloid cells (61%) and the nucleated RBC (32%) comprised over 90% of the nucleated cells in the sternal marrow. The most abundant single cell type was the non-segmented neutrophil (34%), closely followed by the normoblast (31%), after which came the myelocyte (16%) and the segmented neutrophil (7%).

After a week's time the myeloid cells (77%) and the nucleated RBC (12%) still made up almost 90% of the bone marrow cells, but the former group had increased and the latter had dropped sharply. On the 8th day the non-segmented neutrophil (43%) was still in first place, but the myelocyte (20%) had replaced the normoblast (11%) for second place. The segmented neutrophil followed with 10%.

The small percentage of lymphocytes and hematogones increased but slightly by the end of the 1st week of life.

The work of Tecilazic⁵⁹ in 1935, although not strictly comparable because he aspirated tibial marrow, is of great interest. In a small series of cases he compared the marrow picture with the peripheral blood smear. He too found that at birth the myeloid and erythroid elements comprised over 90% of all the nucleated cells; on the 7th day these two groups totalled slightly under 90%. However, in Tecilazic's cases the nucleated RBC (66%) far exceeded the myeloid cells (30%) at birth. On the 7th day he found the relationship to be reversed. Comparing his series with ours, we note:

		Myeloid.	Erythroid.	M/E Ratio.
Tecilazic	1st day	30	66	0.5
	7th day	48	40	1.2
Shapiro and Bassen	1st day	61	32	1.9
	8th day	77	12	6.7

Tecilazic stated that during the first week intense regeneration of the granulocytes occurred, especially among the younger forms (non-segmented neutrophils, myelocytes, and myeloblasts), while in the peripheral blood the granulocytes diminished. The author made no attempt to explain his findings, nor did he investigate the changing red cell picture in the peripheral blood.

Lamy and his coworkers reported sternal marrow findings in the newborn in 1935¹⁸ and in 1939.⁴⁶ In the earlier paper, devoted chiefly to the bone marrow findings in the adult, they stated that no important differences from the adult myelogram were found in infants over 6 months of age. Figures reported for only 1 infant on the 1st day of life showed 45% nucleated RBC. Further investi-

gations were cited in the later paper. Although no tables of figures were given, several interesting conclusions were reached:

1. At birth and during the first few days there are 35-50% nucleated RBC, the great majority of which are normoblasts. At this time, there is a high percentage of granulocytes, especially of the young forms; and the number of lymphocytes is very slight.

2. In the course of the 1st week, the nucleated RBC fall to 25-35%; the granulocytes increase, especially the segmented neutrophils; and the lymphocytes also increase.

Despite the fact that the percentage of nucleated red cells here given is somewhat higher than our own, the above conclusions are in general agreement with our findings, except that we found, as did Tecilazic, that the greatest increase at the end of the week was among the younger granulocytes and not the segmented neutrophils. In 1938 Veeneklaas⁷² reported on the sternal puncture in children, dividing them into various age groups. The investigator felt that Group I, consisting of 3 infants below the age of 14 days, was too small to be of any value statistically. However, it is of interest to note that the average figures for that group are quite similar to our averages for the 8th day.

	Myeloid.	Erythroid.	M/E Ratio
Veeneklaas	67	12	5.6
Shapiro and Bassen	77	12	6.7

Comment. After reviewing the literature, we believe that our findings in the present study lend confirmation to some already established facts and also throw new light on the hematologic picture of the neonatal period.

White Blood Cells. It is reasonable to regard the leukocyte picture at birth as a reflection of hemopoietic hyperactivity during fetal existence. Evidence of this is the high cell count and presence in the blood of immature myeloid cells. It has been assumed that the drop in the white cell count and disappearance of the immature myeloid cells at the end of the first week are peripheral manifestations of decreased *production* of granulocytic leukocytes.⁷ Our bone marrow findings offer another possible explanation for the change which takes place in the white cells. Although the blood differential reveals a shift to lymphocytic predominance at the end of the week, the absolute number of lymphocytes is but slightly higher than in the 1st day of life, whereas the myeloid elements show a marked relative and absolute decrease, with a shift to the right taking place. Since the myeloid cells, especially the younger forms, have actually increased in the bone marrow, it is suggested that during the 1st week of life there is a decreased *release* of the neutrophilic cells into the blood stream.

Red Blood Cells. The high red cell and hemoglobin content of the blood in the 1st day of life is a carry-over from fetal existence.

where low oxygen tension made necessary an abundance of oxygen-bearing cells. Stimulation of hemopoiesis toward this end is seen in the high percentage of nucleated red cells in the sternal marrow and in the peripheral blood findings of normoblasts and an elevated reticulocyte percentage.

At birth, the human organism is cast into a new environment, with the onset of respiration making necessary certain important physiologic changes. Basic needs must be met in a different manner, and the hemopoietic system adjusts itself accordingly.

As the result of some unknown mechanism *the formation of red cells is curtailed*. This is seen by the sharp drop of erythroid elements in the bone marrow and by the decrease of reticulocytes in the peripheral blood.

Many investigators agree with us that some drop in red blood cells and hemoglobin begins during the 1st week of life. On the other hand, the bone marrow findings of decreased red cell production do not necessarily contradict the reports of others^{13,22,24,32,42,48,66,76} who have found a fall in red blood cells and hemoglobin taking place only after the 1st or 2d week; for it is known that changes in the bone marrow may precede peripheral blood changes by a variable length of time. The drop in the reticulocyte percentage during the 1st week is apparently a peripheral reflection of the decreased erythroblastic activity noted in the bone marrow.

The idea of curtailment of red cell formation during the neonatal period is not an original one. Mackay^{49b} suggested it, Josephs^{39a,b} discussed it, and Faxen²⁴ emphasized it.

In 1936 Josephs^{39b} wrote, "One may regard the processes which regulate the level of hemoglobin and red cells as tending to a state of equilibrium which is . . . adjusted . . . at a level . . . that is 'normal' for a given set of conditions. . . . The infant is born with a level of hemoglobin . . . above that which is normal for extra-uterine life. As a result, all signs of regeneration quickly disappear and the hemoglobin falls. . . ." Our point of view is completely in accord with that of Faxen, who said, "To understand all changes in the red blood picture it is important to bear in mind that the percentage of morphological elements and hemoglobin depends on two factors, new formation and destruction. . . . It appears as if the function of the bone marrow . . . has been pushed too much into the background. . . . The rapid fall in the reticulocyte values in the first week of life, found by all investigators, indicates that a reduced new formation of blood cells plays an important part in the change occurring in the blood during the first week."

Heretofore, the neonatal fall in red cells and hemoglobin has generally been attributed to excessive peripheral destruction of the superabundant red cells carried over from fetal life. Evidence in favor of this is by no means universally accepted. On the other

hand, the bone marrow and reticulocyte changes offer clear-cut evidence of diminished red cell formation.

The question arises whether both processes occur at the same time. Although it is possible that following birth some increased peripheral destruction of red cells may take place, the bone marrow evidence of decreasing erythropoietic activity in the 1st week of life could, by itself alone, account for the changes which take place in the red blood cells during this period. These findings suggest that the red cell level falls because of decreased production while the rate of destruction remains constant.

The fact that formation of new red cells by the bone marrow is curtailed may explain why, after birth, there is an increasing deposition of iron in the infant liver.^{1,61} This latter finding has been held as proof of accelerated blood destruction. In contradiction to this idea, however, it is evident that if the bone marrow has cut down on red cell production, it has no great need of the iron derived from red cells which continue to break down.

Conclusions. Peripheral blood studies and sternal puncture examinations were made on 35 normal full-term infants in the 1st 24 hours of life and again 1 week later.

In the peripheral blood our findings agreed with those of many other investigators. We noted initial high levels of RBC, Hb, WBC, and reticulocytes. There was a moderate decrease in RBC and Hb, a sharp fall in WBC and reticulocytes, and a change in the differential from myeloid to lymphocytic predominance at the end of the week.

The most striking finding in the bone marrow was a marked drop in the erythroid elements at the end of the 1st week of life. This finding, reflected in the peripheral blood by the decreasing reticulocytes, is evidence of curtailed production of new red cells. Consequently, we offer the idea that the fall in RBC and Hb which takes place after birth is primarily the result of physiologic disintegration of the superabundant red cells carried over from fetal life, in the presence of diminished erythropoiesis.

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EFFECT OF TOPICAL APPLICATION OF 2-METHYL-1,4-NAPHTHOQUINONE (SYNTHETIC VITAMIN K ANALOGUE) ON THE PROTHROMBIN LEVEL OF NEWBORN INFANTS.

WITH REFERENCE TO A SIMPLIFIED MICRO-PROTHROMBIN TEST.

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HEMORRHAGIC disease of the newborn is now known to be a type of vitamin K deficiency caused by a hypoprothrombinemia which occurs during the first few days of life.^{1,8,14,16} In most newborns physiologic hypoprothrombinemia lasts only a few days and the prothrombin level reaches normal in 6 to 10 days, probably because of the establishment of a bacterial flora in the intestinal tract following the ingestion of food.^{13a,b,14}

The physiologic hypoprothrombinemia of the newborn may be prevented by giving vitamin K orally soon after birth.^{2,5,12,16} The prothrombin level of the newborn may also be increased by giving vitamin K to the mother previous to delivery.^{6,9,15,17} There are obvious disadvantages to both of these methods, such as intolerance to the vitamin or its analogue when given orally or when the onset of labor before the calculated date prevents the timely administration of vitamin K perpartum.

Since vitamin K belongs to the group of fat soluble vitamins (A, D, E and K) it is not unreasonable to suspect that it might be absorbed through the skin. de Beer *et al.*³ have shown that 2-methyl-1,4-naphthoquinone in suitable vehicles administered percutaneously to vitamin K deficient chicks will effect a cure. A single dose of 1 γ per chick cured 50% of the depleted chicks and larger doses afforded protection for relatively long periods of time.

Because of this report it seemed advisable to study the prothrombin levels of the blood of newborns following application of 2-methyl-1,4-naphthoquinone to the skin. A preparation of 2-methyl-1,4-naphthoquinone 1% in a specially prepared base* was used.

Determination of Blood Prothrombin. The difficulty of obtaining sufficient venous blood from newborns in order to obtain plasma for the determination of prothrombin level makes it necessary to use a micro-prothrombin test that employs capillary blood. Several such tests have been described. Quick^{13c} reported a test using 1

* Supplied by Burroughs Wellcome & Co. (U. S. A.), Inc., New York.

drop each of whole blood and thromboplastin. A modification of Quick's original test has been reported by Kato⁷ who used whole oxalated capillary blood to which is added the thromboplastin and calcium chloride solution. White *et al.*¹⁸ reported on a method in which 10 c.mm. of thromboplastin and calcium chloride solution are placed side by side in a hanging drop slide and 10 c.mm. of blood obtained by puncture is added and mixed. A simple method described by Lawson,¹⁰ employs a specially prepared thromboplastin solution. The blood obtained by puncture is added directly to the thromboplastin solution in the well of a hollow-ground slide.

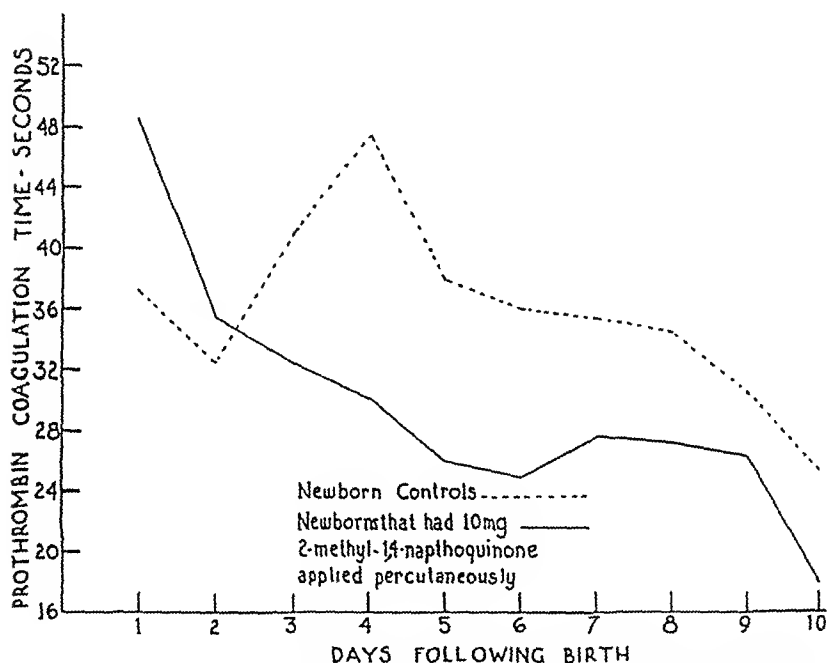


FIG. 1.—Average prothrombin coagulation time of a group of newborn infants and of a similar group that had 10 mg. 2-methyl-1,4-naphthoquinone applied percutaneously during the first 48 hours following birth.

Simplified Method of Micro-prothrombin Determination. Previously we reported¹¹ on a simplified method of determining the prothrombin level in oxalated plasma by substituting Russell viper venom for the thromboplastin solution obtained from rabbit brain such as is used in Quick's method.

This method has been adapted for use with small amounts of capillary blood and has been satisfactory for use in determining prothrombin levels in newborn infants.

The test can best be performed in the nursery at the newborn's bedside. The newborn's heel or toe is cleaned with alcohol and a deep puncture is made with a lancet or needle so that the blood flows freely. Twenty cubic millimeters of blood is drawn into a hemoglobin pipette and immediately placed in the well of a hollow-

ground slide that contains 0.0274 mg. potassium oxalate.* (The slides are previously prepared by placing in the well of each slide the solution of potassium oxalate and allowing it to dry.)

The blood is thoroughly mixed with the oxalate and to it is added 20 e.mm. of a 1 to 10,000 dilution of Russell viper venom† and 20 e.mm. of 1.11% calcium chloride solution. The slide is tilted from side to side and the end-point is taken at the moment that fibrin clots can be seen. The end-point is usually sharp and the prothrombin time is considered to be the number of seconds from the addition of the calcium chloride solution to the formation of fibrin clots. We consider the normal prothrombin coagulation time, by this method, to be 28 seconds or less.

The above test was performed on 48 newborn infants divided into two equal groups. One group served as control and the other group received one application of 10 mg. 2-methyl-1,4-naphthoquinone in an ointment base applied topically to the back. Usually the vitamin K ointment was applied during the first or second day following birth. Micro-prothrombin estimations were performed 3 times a week on each newborn infant during its period of hospitalization. Each newborn had 4 or 5 prothrombin estimations during the period of observation.

Results. The typical physiologic hypoprothrombinemia of the newborn was exhibited in 18 of the 24 newborns in the control group (Table 1). The highest prothrombin coagulation time was present on the 4th day of life and decreased to the normal level at the 8th to 10th day with the exception of Case 21 which was 40 seconds on the 10th day.

The group that had 10 mg. 2-methyl-1,4-naphthoquinone applied to the skin of the back on the 1st or 2d day of life did not show any increase in prothrombin coagulation time (Table 2). The prothrombin coagulation time showed a steady decrease and was within normal limits by the 5th day. No newborn treated in this manner exhibited the so-called physiologic hypoprothrombinemia.

In order to determine if the average prothrombin coagulation observed for the two groups on the 4th day were significantly different, the "t" value was obtained and found to be 7.6‡ which

* Potassium oxalate solution was prepared by diluting 1 cc. 20% solution potassium oxalate to 450 cc. with distilled water. This represents approximately 0.0274 mg. per minim, and was found to be sufficient to prevent coagulation of the whole blood.

† Russell Viper Venom ("Stypven") supplied by Burroughs Wellcome & Co. (U. S. A.), Inc., New York.

$$\dagger \text{ "t" } = \frac{\bar{X}_c - \bar{X}_t}{S \sqrt{\frac{1}{N_c} + \frac{1}{N_t}}} = \frac{47.38 - 29.96}{11.03 \sqrt{\frac{1}{12} + \frac{1}{8}}} = 7.6$$

\bar{X}_c = Average prothrombin coagulation time of control newborns.

\bar{X}_t = Average prothrombin coagulation time of treated newborns.

S = Sum of squares of deviations from respective means.

N_c = Number of cases in control group.

N_t = Number of cases in treated group.

corresponds to probability greater than 0.001 according to the tables of Fisher and Yates.⁴ It follows that when the difference between the two means is 7.6 times as great as the standard error, the difference observed between the treated and the control newborns is not accidental but is the result of some definite cause, being, in this study, the percutaneous administration of 2-methyl-1,4-naphthoquinone ointment.

TABLE 1.—PROTHROMBIN COAGULATION TIMES OF NEWBORN CONTROLS.

Days after birth:	1	2	3	4	5	6	7	8	9	10
Prothrombin time: Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.
Case No.										
1	35.0	31.0	34.0	51.1	53.0	32.2	29.5	36.0	32.4	26.0
2	26.8	31.3	75.8	55.0	42.0	33.5	32.8	31.6	30.0	20.3
3	19.1	44.4	59.0	41.5	34.0	22.1	39.1	30.4	22.7	30.6
4	31.8	30.8	41.6	33.2	39.8	28.0	39.1	25.0	18.0	25.6
5	22.8	32.5	33.2	28.0	39.8	39.1	25.0	18.0	25.6	25.6
6	33.0	46.0	65.7	36.0	29.7	36.4	26.5	30.6	18.0	25.6
7	49.7	39.2	34.7	41.8	23.8	37.4	25.6	30.6	18.0	25.6
8	30.0	27.0	43.5	55.5	40.0	42.0	29.0	40.0	29.0	29.0
9	30.0	27.0	43.5	55.5	40.0	42.0	29.0	40.0	29.0	29.0
10	52.0	30.2	31.0	34.6	34.0	33.2	59.0	45.0	40.0	40.0
11	34.2	30.2	31.0	34.6	34.0	33.2	59.0	45.0	40.0	40.0
12	50.0	30.2	31.0	34.6	34.0	33.2	59.0	45.0	40.0	40.0
13	47.0	30.2	31.0	34.6	34.0	33.2	59.0	45.0	40.0	40.0
14	24.0	30.2	31.0	34.6	34.0	33.2	59.0	45.0	40.0	40.0
15	26.5	30.2	31.0	34.6	34.0	33.2	59.0	45.0	40.0	40.0
16	58.6	30.2	31.0	34.6	34.0	33.2	59.0	45.0	40.0	40.0
Average	37.1	32.4	41.1	47.4	37.8	36.0	35.4	34.5	30.3	25.4

TABLE 2.—PROTHROMBIN COAGULATION TIMES OF NEWBORNS THAT RECEIVED 10 MG. 2-METHYL-1,4-NAPHTHOQUINONE PERCUTANEOUSLY.

Days after birth:	1	2	3	4	5	6	7	8	9	10
Prothrombin time: Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.	Sec.
Case No.										
1	30.8	34.0	29.8	21.4	29.0	26.4	31.2	29.6	18.0	18.0
2	50.4	30.1	22.6	28.9	26.4	31.2	29.6	18.0	18.0	18.0
3	53.0	33.7	25.2	32.6	24.0	31.2	29.6	18.0	18.0	18.0
4	34.4	23.3	18.2	24.0	31.2	29.6	18.0	18.0	18.0	18.0
5	31.2	27.0	22.1	22.1	31.2	29.6	18.0	18.0	18.0	18.0
6	38.7	33.4	29.0	27.5	28.9	29.6	18.0	18.0	18.0	18.0
7	37.0	33.0	27.5	27.5	28.9	29.6	18.0	18.0	18.0	18.0
8	36.2	36.0	23.6	23.6	26.5	29.6	18.0	18.0	18.0	18.0
9	57.7	38.2	23.1	23.1	22.5	29.6	18.0	18.0	18.0	18.0
10	47.0	26.1	27.6	27.6	30.0	29.6	18.0	18.0	18.0	18.0
11	57.0	51.6	28.5	41.0	26.8	29.6	18.0	18.0	18.0	18.0
12	41.1	29.5	28.5	28.5	24.0	29.6	18.0	18.0	18.0	18.0
13	42.0	32.0	29.3	28.2	28.4	29.6	18.0	18.0	18.0	18.0
14	40.0	33.0	28.2	28.2	27.0	29.6	18.0	18.0	18.0	18.0
15	50.0	30.5	21.5	21.5	30.1	29.6	18.0	18.0	18.0	18.0
16	60.1	32.0	27.5	27.5	26.2	29.6	18.0	18.0	18.0	18.0
17	32.4	28.2	22.0	22.0	19.0	29.6	18.0	18.0	18.0	18.0
18	97.0	38.4	35.0	35.0	44.5	29.6	18.0	18.0	18.0	18.0
19	47.6	27.3	25.0	25.0	28.0	29.6	18.0	18.0	18.0	18.0
20	92.0	42.2	21.6	21.6	24.4	29.6	18.0	18.0	18.0	18.0
21	26.0	25.1	21.0	21.0	23.0	29.6	18.0	18.0	18.0	18.0
22	47.0	23.0	19.2	19.2	20.1	29.6	18.0	18.0	18.0	18.0
23	31.0	26.2	26.0	26.0	24.0	29.6	18.0	18.0	18.0	18.0
Average	48.3	35.5	32.5	30.0	25.7	24.8	27.7	27.2	26.6	18.0

No untoward effects from the 2-methyl-1,4-naphthoquinone ointment were observed in any newborn.

Summary and Conclusions. A simplified micro-prothrombin test has been described which has obvious advantages over methods that employ unstable thromboplastic substances. The Russell viper

venom used as the thromboplastic agent is stable for several weeks when kept in a refrigerator and does not require time-consuming laboratory preparation. We believe that this simplified test which requires no special apparatus or unstable reagents can be performed by the practitioner at the bedside.

Data have been presented in this study showing that the percutaneous application of 2-methyl-1,4-naphthoquinone (Synthetic Vitamin K analogue) in an ointment base will prevent hypoprothrombinemia of the newborn. As this method is simple and effective it is suggested that it be used routinely as a prophylactic measure in preventing hypoprothrombinemia of the newborn. As a routine procedure 10 mg. of 2-methyl-1,4-naphthoquinone in a special ointment can be rubbed thoroughly on the skin of the back during the 1st or 2d day of life. As a single application was effective in our series we do not believe that the application need be repeated.

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THE EFFECTIVENESS OF PRENATAL ADMINISTRATION OF 2-METHYL-1, 4-NAPHTHOQUINONE IN MAINTAINING NORMAL PROTHROMBIN LEVELS IN INFANTS.*

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Two factors have contributed to more complete understanding and effective treatment of hemorrhagic diseases in infants: the

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introduction of accurate micro methods of determining the prothrombin level of the blood, and the discovery that vitamin K is a potent factor in maintaining a normal prothrombin level. This led in turn to the discovery that the prothrombin time tends to be greatly prolonged in infants showing hemorrhagic manifestations, in which case the administration of vitamin K to such infants results in rapid improvement and establishment of a normal prothrombin level.

In spite of considerable variation in methods and results, a number of facts have been established. First, in newborn infants the prothrombin level during the first 24 hours appears to be within normal limits or slightly under normal, with a fall to a definitely low level between the second and the fourth days.^{1,2,4,7-10,12,14,19a} A gradual return to normal or almost so occurs at the end of a week or 10 days. Although the prothrombin may fall to a very low level, hemorrhagic manifestations do not necessarily occur.⁹ Furthermore, direct treatment of newborn infants with vitamin K by mouth results in a prompt increase of the prothrombin to normal, or if given early enough, in prevention of the usual drop of the prothrombin level.^{4,8-10,12,13,17,19a}

Evidence has been presented^{3-5,10,11,17,18,19b,20} that treatment of the mother with vitamin K helps in maintaining a normal prothrombin level in the infant. The results, however, are not entirely conclusive since in most instances prothrombin was determined on the first day of life only. Since relatively high prothrombin levels existing on the first day of life are followed by a distinct drop, usually on the second day, the results cannot be properly evaluated unless observations are continued through this more critical period. A number of the reports cited deal with small numbers of subjects.

The investigation reported here was undertaken in order to determine the efficiency of 2-methyl-1, 4-naphthoquinone, one of the synthetic forms of vitamin K, in maintaining normal prothrombin levels in newborn infants when given to the mothers during the last weeks of pregnancy. A second objective was to ascertain the extent of the need for vitamin K therapy during pregnancy in the population served by this institution: the unemployed, laboring, and lower middle classes of the eastern industrial region.

Methods and Materials. Prothrombin was determined in plasma of 25 infants whose mothers had received tablets* containing 2 mg. of 2-methyl-1, 4-naphthoquinone together with 0.2 gm. of purified bile salts daily by mouth for varying periods of time during the last month of pregnancy. Twenty-five infants whose mothers received no treatment were used as controls. Plasma prothrombin of the infants was determined on the first day, between the second and fourth day, and again on the sixth or seventh day after delivery. Cases were chosen at random from patients registered in the prenatal clinic during October, November, December, and January. No untoward reactions were observed in the treated patients.

* Supplied by Jovan Laboratories, Inc.

Because of the technical difficulties of obtaining venous blood from newborn infants, the micro method devised by Hoffman and Custer⁶ was used as follows: 5 c.mm. of blood obtained from the finger or heel was immediately transferred by means of a Custer hemoglobin pipette to a glass culture slide containing 5 c.mm. of a saline suspension of thromboplastin maintained at 37° C. on a hot plate. The mixture was then gently and slowly stirred with a platinum wire, and the time necessary for coagulation ascertained by means of a stop watch. All determinations were made in duplicate and the average taken. The variation was small. A fresh puncture was made for each determination, a spring lancet being used to insure a free flow of blood. A control was run in every case, using in most instances the same normal individual. The thromboplastin was prepared by Quick's¹⁵ method.

Control determinations by this method showed the average prothrombin time to be 12.7 seconds. These figures are based on 48 different determinations made on 4 normal individuals. Results of determinations on normal subjects by Quick's method showed close agreement with those of the Hoffman-Custer method. In order to correct for the varying potency of the thromboplastin (thromboplastin emulsion was prepared freshly each day), the following formula¹⁶ was used:

$$\frac{\text{prothrombin time of infant} \times 12.5}{\text{prothrombin time of control}} = \text{corrected prothrombin time.}$$

The corrected prothrombin time was then converted to prothrombin percentage of normal by means of the graph published by Quick.^{11b}

TABLE 1.—THE PLASMA PROTHROMBIN OF 25 UNTREATED CASES.
Prothrombin, % of normal.

Case No.	Mother.	Infant.		
		1st day.	2d-4th day.	6th-7th day.
1	60	..	70	100
2	85	..	9	60
3	100	30	30	45
4	95	..	40/35	100
5	95	100	40	..
6	98	..	25	100
7	55	16	8	80
8	100	..	40	..
9	65	45	33	85
10	100	100	37	..
11	100	100	69	100
12	100	45	43	33
13	65	37	8	..
14	100	90	65	100
15	100	67	70	85
16	75	100	60	..
17	100	100	100	..
18	100	85	40	100
19	90	70	38*	60*
20	70	90	33	100
21	80	67	40	100
22	100	90	33	37
23	65	53	45	63
24	100	95	37	40
25	75	70	60	..
Average	88	72	43	77

* Vaginal bleeding, 3d to 5th day.

Results. Tables 1 and 2 show the plasma prothrombin levels expressed as per cent of normal of 50 untreated pregnant women, 25 in the control group and 25 in the treated group. The average value of 89 per cent for this entire group may be taken as a normal standard for this study. It may be seen in Table 2 that there is no significant difference in the average prothrombin level of the mothers before and after receiving treatment with 2-methyl-1, 4-naphthoquinone.

On the first day of life, infants of untreated mothers (Table 1) show an average prothrombin of 72%, as compared with an average value of 86% for infants whose mothers received treatment with vitamin K (Table 2). This difference is not significant.*

TABLE 2.—THE PLASMA PROTHROMBIN OF 25 TREATED CASES.

Case No.	Duration of treatment (days).	Prothrombin, % of normal.				
		Mother.		Infant.		
		Before treatment.	After treatment.	1st day.	2d-4th day.	6th-7th day.
1†	20	100	100	(40)	(48)	..
2	7	80	95	82	100	100
3	21	80	100	80	70	..
4	12	90	90	80	90	100
5	6	80	90	100	85	100
6	17	100	100	35	58	100
7	25	100	60	..	85	85
8	?	50	75	..	78	85
9	21	100	99	100	50	45
10	11	100	100	60	100	..
11	28	98	100	90	100	100
12	17	100	70	75	83	..
13	9	98	100	99	100	100
14	20	100	75	..	70	100
15	12	70	100	100	90	100
16	10	100	100	100	100	90
17	9	90	100	100	100	85
18	20	100	100	100	100	..
19	10	85	85	85	100	100
20	5	100	100	100	85	..
21	24	100	100	85	70	70
22*	24‡	100	100	(85)	(45)	(55)
23	10	90	85	..	100	100
24	9	65	95	70	85	..
25	15	70	80	..	80	90
Average		90	92	86	86	89

During the second to fourth day period the infants whose mothers had received no treatment showed a distinct drop of the prothrombin level to an average value of 43% (Table 1). The corresponding value for infants of treated mothers was 86% (Table 2). This difference is highly significant.* Individual values in the untreated

* Tested by Student's method for determining "t".

† Omitted from calculation of mean

‡ No medication for 2 weeks prior to delivery.

group ranged from 8 to 100%, with only 4 cases having prothrombin levels above 65%. In the treated group, prothrombin ranged from 50 to 100% with only 4 patients showing less than 70%.

By the sixth to seventh day, the average prothrombin level had increased to 77% in the untreated cases, and 89% in the treated cases. Although this difference is not significant,* 7 of 18 determinations made at this time on untreated infants gave results below normal and in 4 the deficiency was marked. In the treated group only 2 cases fell below 70%.

Of the 4 infants in the treated group that showed abnormally low prothrombin levels, the mother of one (Case 1) was thought to have been uncoöperative in taking the medication, while another (Case 22) finished her supply 2 weeks before delivery and did not return for more. Consequently both were omitted in calculating the average values. No reason for failure could be found in Cases 6 and 9.

Discussion. Infants from untreated mothers having normal prothrombin levels usually exhibit a normal level during the first day of life. The prothrombin rapidly falls to an abnormally low level after the first day, but by the end of the first week has in most cases again risen to normal. This drop varies in degree. A low prothrombin level alone does not seem to be sufficient to induce spontaneous hemorrhage, since only one baby of those with dangerously low prothrombin showed such a tendency.

Prothrombin remained normal with few exceptions in those infants whose mothers received vitamin K during the last weeks of pregnancy, if only for so short a period as 5 days. In 2 of 4 infants failing to show a response to prenatal therapy there were circumstances indicating that the failure was not due to the ineffectiveness of the drug.

These results are compatible with the assumption that the newborn infant is endowed with sufficient prothrombin to last for approximately 24 hours, and is then faced with an interval when, due to lack of an adequate supply of vitamin K, this inherited prothrombin is used up without sufficient new being formed. Soon after the infant begins to take and absorb nourishment a normal level is built up by the liver, although in most cases a week is required before normal levels are established. It seems probable that in infants whose mothers have received vitamin K therapy a sufficient amount of this substance is carried over in the fetal blood supply to tide the infant over the danger period and allow the earlier production of prothrombin by its own liver.

The effectiveness of 2-methyl-1, 4-naphthoquinone administered prenatally for maintenance of normal prothrombin in the newborn is demonstrated by this study.

Summary. 1. About $\frac{3}{4}$ of the infants of untreated mothers exhibited a significant drop to an abnormally low average prothrombin level

* Tested by Student's method for determining "t".

within 48 to 96 hours after birth, with a rise to a normal level by the end of the first week.

2. Infants whose mothers had received 2-methyl-1, 4-naphthoquinone from 5 to 28 days prior to delivery were protected against the fall in prothrombin in all but 2 of 23 cases.

3. Occasional subnormal prothrombin levels were observed in a group of 50 pregnant women examined shortly before term.

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PERIPHERAL CIRCULATORY FAILURE IN DIABETIC ACIDOSIS AND ITS RELATION TO TREATMENT.*

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THE presence of peripheral circulatory failure in diabetic acidosis has been recognized clinically for many years. Fagge,⁷ in 1874, described a case of acidosis which improved after the intravenous administration of saline solution. Peters^{15,16} has attributed to the

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shock syndrome certain chemical changes* in diabetic acidosis. In 1928, Allen¹ called attention to the clinical picture of "shock" in diabetic acidosis of long standing. Atchley,^{2a} in 1930, used the term "medical shock" to describe the clinical picture of severe diabetic acidosis. In 1930, Lawrence,¹³ and in 1934, Atchley² re-emphasized the importance of treatment of "medical shock" in diseases, notably diabetic acidosis, associated with marked dehydration.

The clinical picture of patients who are moribund in uncomplicated diabetic acidosis is characterized by a rapid pulse of poor volume, a falling blood pressure, a rising body temperature, deepening unconsciousness ending in death. This sequence of events occurs despite treatment with insulin, glucose, alkalies and fluids. Death may occur while the blood sugar concentration and CO₂ combining power values are nearly normal. If the alterations in blood sugar concentration and CO₂ combining power represent the metabolic disturbances responsible for the condition of these patients, why should they die when the metabolic disturbances, as represented by these chemical data, are corrected?

Postmortem examination of patients dying in uncomplicated diabetic acidosis affords little help in establishing the mechanism of death. Warren's¹⁸ description of the pathologic findings in cases of diabetic acidosis can be summarized by the following quotations: "The pathological changes in coma are conspicuous by their absence. Even in pre-insulin days when diabetic coma developed in uncomplicated cases of diabetes there were no characteristic pathological changes that would enable one at post mortem or on looking at a section of tissue to say 'This material came from a case of diabetic coma.' Today the same holds true." The only constant finding was evidence of gastro-intestinal hemorrhage. Dillon, Riggs and Dyer⁶ described brain lesions in "fatal diabetic acidosis like those seen in acute asphyxia. The primary pathologic changes occur in the cerebral capillary bed. The capillaries are dilated, and the endothelial cells show degenerative changes with increased permeability of the walls as evidenced by the presence of perivascular and pericellular edema. As a result of the cerebral edema there is proliferation of neuroglia, especially in the subependymal and marginal areas, and acute degenerative changes in the ganglion cells."

Since death frequently occurs in these patients whose diabetic chemically disordered function has been corrected by treatment, and postmortem examination of these patients yields little evidence in establishing a mechanism for death, it seemed reasonable to look for a disturbance of function which might be sufficient to cause death and yet not leave diagnostic postmortem changes. The clinical impression of Allen, Peters, Atchley and others of the existence of "medical shock" in diabetic acidosis and the clinical picture of peripheral circulatory failure which we have also observed

* Serum proteins, blood cell volume and oxygen capacity.

suggested the direction for the investigation of the disturbance of function.

Methods. The patients studied were selected from those admitted in diabetic acidosis to the Metabolic Division of the Philadelphia General Hospital, services of Dr. E. S. Dillon and Dr. A. J. Sindoni, Jr.

Temperature, pulse rate, blood pressure and respiratory rate were recorded every half hour. Blood sugar and CO₂ combining power determinations were made on admission and were repeated every 3 hours throughout the course of treatment until recovery or death had occurred. Blood sugar determinations were made by a modified method of Folin and Wu and CO₂ combining power of plasma was determined by the method of Van Slyke and Cullen.^{14a}

Blood for examination was drawn without stasis from the femoral artery and vein in oiled syringes and placed in tubes containing potassium oxalate and paraffin oil. Arterial and venous oxygen content, CO₂ content, and oxygen capacity were determined by the method of Van Slyke and Neill.^{14b} Serum proteins, hemoglobin and cell volume by hematocrit were measured. Kingsley's photoelectric biuret¹² method was used for serum protein, and the Sanford, Sheard and Osterberg photo-electric colorimetric method¹⁷ was used for CO_2 combining power determinations. Packed cell volume measurements were made in hematocrit tubes after centrifuging for 30 minutes. These studies were repeated during the course of treatment and again after recovery.

Peripheral bloodflow in the hand was measured by the plethysmograph and was recorded soon after admission and as often as possible thereafter until recovery or death. Freeman's modification^{5a} of the original method of Hewlett and Van Zwahlenburg was used.

Results. One group of patients with diabetic acidosis had a reduced peripheral circulation which, however, was compensated and recovered following treatment. These patients were conscious, had little or no reduction in blood pressure and had moderate reductions in peripheral bloodflow. Figure 1 shows the course of such a patient. This patient was admitted to the hospital in acidosis after a dietary indiscretion with a blood pressure of 130/70 mm. of mercury, a pulse rate of 116 per minute, and a reduced bloodflow (3.6 to 5.7 cc./100 cc. of hand per minute). The venous oxygen saturation was 88.8% on admission but during treatment fell to 59.5%; after recovery it was 86%. The patient absorbed fluids given by hypodermoclysis and showed an increased bloodflow before intravenous fluids were given. Treatment was accompanied by an increase in peripheral bloodflow and a decrease in venous oxygen saturation.

A second group had diabetic acidosis with peripheral circulatory failure and recovered after treatment. They were semiconscious or unconscious, had marked reduction in blood pressure and peripheral bloodflow. The course of one is shown in Figure 2. This patient was a newly discovered diabetic in whom acidosis was probably precipitated by pharyngitis with cervical adenitis. On admission to the wards his blood pressure was 50/30 mm. of mercury, pulse rate 120 per minute, peripheral bloodflow was not recordable, and

venous oxygen saturation was 63.8%. Plasma and 6% acacia were given before bloodflow could be recorded. The bloodflow increase and the rise in blood pressure were maintained. The patient

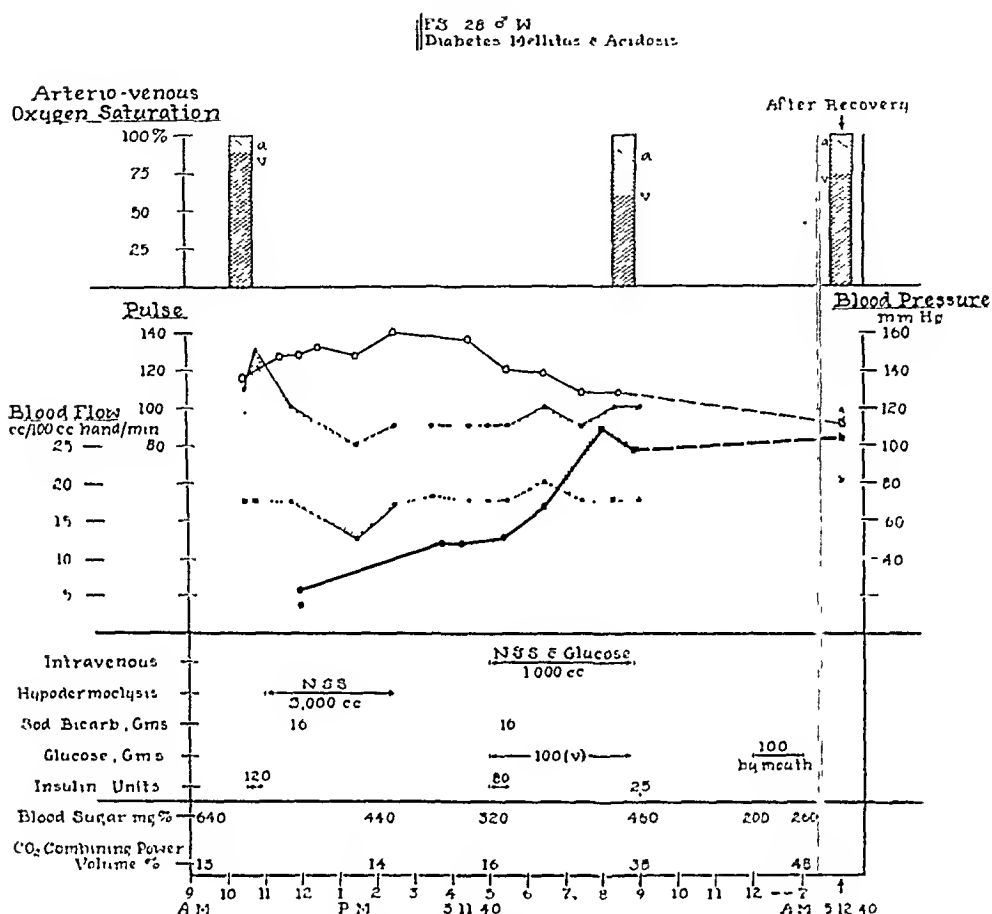


FIG. 1.—Diabetic Acidosis—Peripheral Circulation Compensated (Recovered): Course of Case 2.

On admission: The patient was conscious. He had a moderately reduced peripheral circulation but a maintained blood pressure. Venous oxygen saturation was 88.8%.

During treatment: Peripheral bloodflow increased and was maintained following the administration of saline solution by hypodermoclysis. The intravenous infusion was given to supply glucose rather than to increase circulation. Venous oxygen saturation decreased while peripheral bloodflow increased during treatment. The general condition of the patient was more closely correlated with the state of the circulation than with the level of the CO₂ combining power.

Abscisse: Time in hours.

Ordinates: Blood sugar concentration and CO₂ combining power values. Treatment administered and time required for each item of treatment. Peripheral bloodflow, pulse rate, blood pressure and arterial and venous oxygen saturation.

became conscious soon after the rise in blood pressure and bloodflow. This took place 4 hours after treatment was started but long before the blood ketone body level fell. During treatment the venous oxygen saturation was 68%. After recovery the venous-

oxygen saturation was 78% in the presence of a rapid bloodflow. The presence of a venous oxygen saturation of 63.8% with marked reduction of bloodflow in this patient, in contrast to the venous oxygen saturation of 88.8% with less marked reduction in bloodflow in the case shown in Figure 1, may be the result of a more advanced state of peripheral circulatory failure.

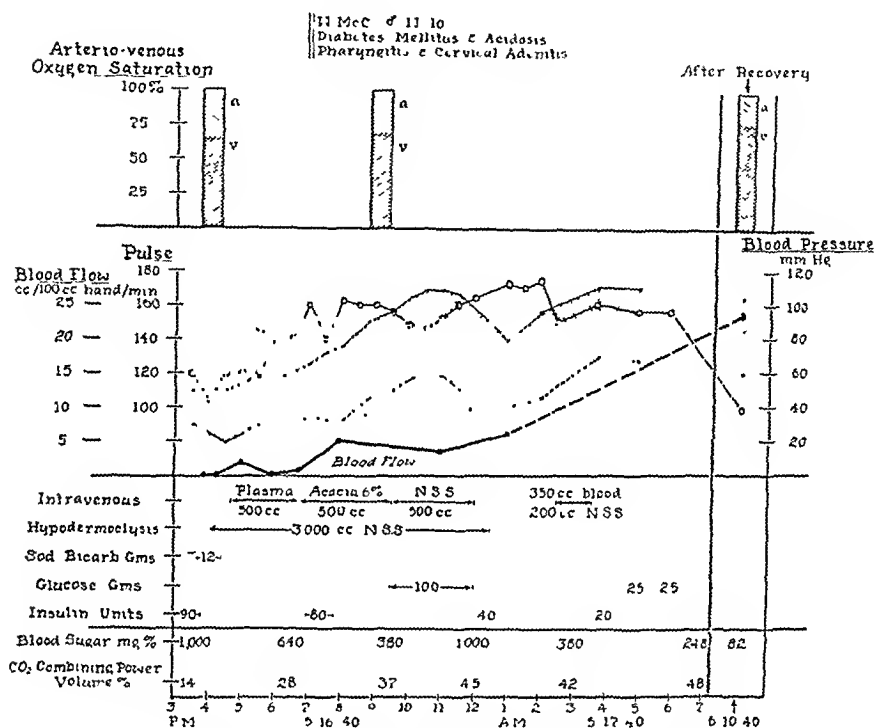


FIG. 2.—Diabetic Acidosis With Peripheral Circulatory Failure (Recovered): Course of Case 6.

On admission: The patient was unconscious, his extremities were cool and his skin was mottled. Blood pressure and peripheral bloodflow were markedly reduced. Venous oxygen saturation was 63.8% in the presence of a reduced circulation.

During treatment: Peripheral bloodflow and blood pressure were increased and maintained only after the administration of osmotically active fluids by the intravenous route. The patient regained consciousness at 7:30 P.M., coincident with an increase in peripheral bloodflow and blood pressure. Venous oxygen saturation was 68% in the presence of an increased circulation. The general condition of the patient was closely correlated with the state of the circulation.

Abscissæ and ordinates as in Figure 1.

A third group had diabetic acidosis with peripheral circulatory failure but died despite treatment. Figure 3 shows the course of one of these patients who had lost consciousness and showed marked reduction in blood pressure and bloodflow. This patient had a cellulitis of the neck which was probably responsible for the onset of acidosis. On admission to the wards, the blood pressure was 68/40 mm. of mercury, pulse rate 116 per minute, bloodflow 1.2 cc./100 cc. of hand per minute, and the venous oxygen saturation was

64.2%. Blood pressure and blood flow rose only after administration of 6% acacia intravenously. This increase was not maintained. Here again, the venous oxygen saturation of 64% contrasted to venous oxygen saturations of 83% to 88.8% in patients with the same degree of reduction of bloodflow may indicate a more severe failure of the peripheral circulation.

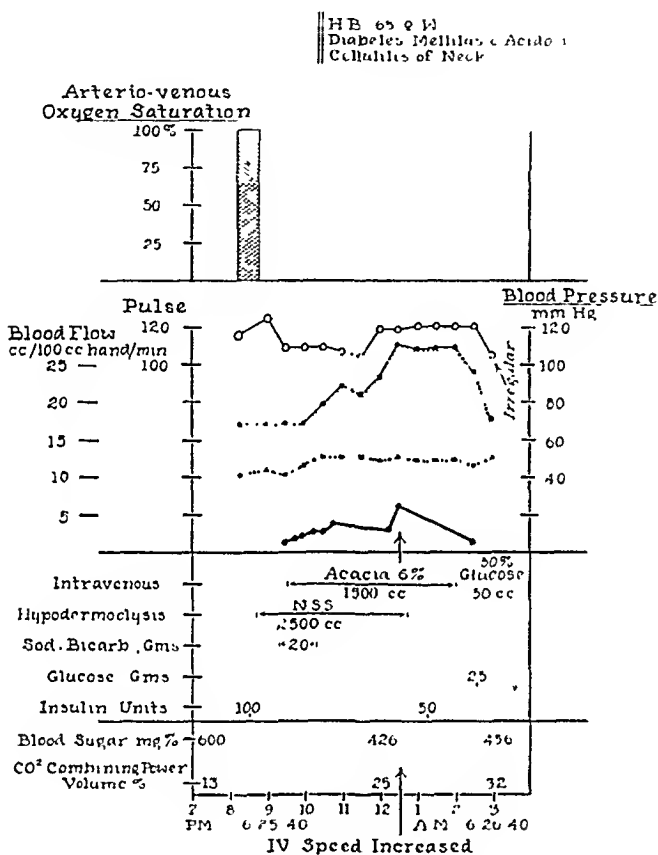


FIG. 3.—Diabetic Acidosis With Peripheral Circulatory Failure (Died):
Course of Case 7.

On admission: The patient was unconscious. She had a marked reduction of peripheral bloodflow and blood pressure. Venous oxygen saturation was 64.2%.

During treatment: There was a failure to maintain an increased peripheral bloodflow and blood pressure despite the administration of osmotically active solutions by the intravenous route. The CO₂ combining power values rose during treatment. This case likewise illustrates the close correlation between the general condition of the patient and the state of the circulation.

Abscisse and ordinates as in Figure 1.

The findings obtained in all of the patients studied are summarized in Table 1. Peripheral bloodflow was reduced in all patients on admission. The patients with the most marked reductions were most seriously ill, were unconscious and had lowest blood pressures. Bloodflow increased markedly during treatment. Sudden marked increases in flow were usually associated with increase in speed of intravenous infusion.

TABLE 1.—SUMMARY OF RESULTS.

SUMMARY OF RESULTS.																						
Patient.	Date, 1940.	Time.	Serum proteins, gm. per 100 cc.		Hemoglobin, gm. per 100 cc.		Hematocrit, %.		Blood sugar, mg. per 100 cc.	Blood CO ₂ content, vol. %.		Oxygen content, vol. %.		Oxygen capacity, vol. %.		Oxygen saturation, %.		Blood pressure, mm. mercury.	Blood flow, cc. blood per 100 cc. hand per minute.	Oxygen utilization, cc. oxygen per 100 cc. hand per min.	Mental state.	
			Arterial.	Venous.	Arterial.	Venous.	Arterial.	Venous.		Arterial.	Venous.	Arterial.	Venous.	Arterial.	Venous.							
I. J. McD.																						
31 M W																						
Group I. PERIPHERAL CIRCULATION COMPENSATED. Recovered.																						
	4/6	12:00 N. on adm.	10 3	9 9	16 9	16 7	55 8	57 5	820	13 4	15 4	21 8	19 1	22 6	22 4	86 4	85 3	100/70	3 9	0 11	Conscious	
	4/6	6:00 P.M. during treat.	9 9	9 0	16 7	16 7	58 1	56 3	440	31 1	37 2	10 8	14 0	22 2	22 4	80 2	82 5	100/80	5 2	0 48	Conscious	
	4/8	8:00 P.M. after recov.	5 5	5 4	14 0	14 1	41 0	42 5	163	52 0	55 1	17 0	13 5	18 7	18 0	90 0	71 4	5 5	0 25	Conscious	
2. F. S.																						
28 M W																						
	5/11	10:30 A.M. on adm.	9 4	0 3	18 0	50 0	640	6 0	11 0	23 7	20 3	24 2	97 8	88 8	120/70	3 7	0 12	Conscious	
	5/11	8:30 P.M. during treat.	7 4	7 3	16 0	16 1	45 4	46 3	460	30 2	35 8	20 6	13 4	22 5	91 5	59 5	120/70	27 1	1 95	Conscious	
	5/12	11:15 A.M. after recov.	7 2	7 3	15 0	15 1	41 0	41 6	260	40 6	41 3	19 7	17 4	20 3	97 0	85 6	118/80	22 6	0 52	Conscious	
3. R. C.																						
36 M B																						
Group II. PERIPHERAL CIRCULATORY FAILURE. Recovered.																						
	5/30	10:45 P.M. on adm.	8 1	8 0	16 1	16 2	31 4	616	5 8	7 5	20 7	18 3	21 5	96 3	85 1	88/52	1 0	0 02	Semiconscious	
	5/31	4:15 A.M. during treat.	7 6	7 6	14 8	14 9	28 2	31 5	330	19 1	24 2	19 5	14 2	10 9	97 8	71 3	122/80	6 9	0 37	Conscious	
	6/11	8 00 P.M. after recov.	7 4	13 2	25 0	118	34 6	42 8	16 9	9 5	17 8	94 5	53 3	94/64	3 2	0 24	Conscious	

1 H. L. 61 F W	1/22	8 15 P.M. on adm.	8 8 8 7	11 6	11 2	36 5	35 0	800	4.1	6 7	14 0	12 5	15 5	15 0	90 0	83.3	92/40	3 8	0 04	Unconscious
										6 7†		12 5†								
	1/23	3:30 A.M. during treat.	5.8 5 4	9 5	9 2	21.7	21 3	400	24.2	25 0	10.8	9 1	12 7	12 3	84 7	73 8	120/60	32 8	0 56	Semiconscious
										25 8†		9 3†								
	1/23	3 30 P.M. during treat.	1 8 4.5	10.5	10.5	29.3	26 2	370	43 0	46 8	13 0	11 3	14 1	14.1	92 3	80 3	21 6	0 37	Conscious
	5/9	10 00 P.M. after recov.	6.5 6 9	16 2	10 5	29.5	32 6	228	42.2	48 7	11 2	11 6	120/60	17 6	0 47	Conscious
										49 5†		11 2†								
5. R. W. 18 F W	6/19	6 00 P.M. on adm.	7.1 6 9	9.5	17 9	21 9	600	6 4	8 6	12 0	10 7	12.8	93 7	83 5	76/44	1 2	0 03	Unconscious
	6/19	10 30 P.M. during treat.	5 0 1 7	10.3	22 5	23 7	169	15 1	19 2	11.8	8 8	12 5	91 3	70 4	118/88	3 4	0 10	Conscious
	7/8	9 30 P.M. after recov.	6 8 6 2	11 9	11 8	21 6	26 9	320	16 2	Conscious
	7/12	After recov.	236	47 0	51 0	13 7	11 8		14 2	96 5	83 1	130/84	12 9	0 24	Conscious
6. W. McC. 10 M W	5/16	1 00 P.M. on adm.	7 9 7 8	11.7	11 6	11 5	42 8	1000	7 1	11 9	19 4	12 7	.	19 9	97.5	63 8	50/30	0 0	0 0	Unconscious
	5/16	9 00 P.M. during treat.	5 2 5 0	13 7	13 6	380	27 8	32 6	17 8	12 6	18 5	96 3	63 0	76/34	7 0	0 36	Semiconscious
	6/10	9 30 P.M. after recov.	6 3 .	.	10 8	35 3	...	60	16 0	50 3	11 2	11.1	11 6	97.3	78 0	101/60	23.6	0 66	Conscious
7. H. R. 65 F W	6/25	8 30 P.M. on adm.	6 7 6 8	16 6	11 8	33 8	32 3	600	6.3	12 0	17 9	12 2	19 0	94 4	64 2	68/10	1 2	0 07	Unconscious
8. F. W. 38 M B	8/18	7 00 P.M. on adm.	7 8 8 0	19 0	.	33 0	31 0	610	8 8	11 1	23 9	11 4	25 1	...	95 2	45 2	96/70 121/70	3 7	0 16	Unconscious Unconscious

GROUP III PERNICIOUS CIRCULATORY FAILURE. D.I.O.

* Blood sugar determinations were not always made at the same time as the other studies. The values given are those obtained nearest the times listed.

† The blood drawn from superficial antecubital vein of arm in plethysmograph for comparison with femoral vein blood.

‡ Studies were made about 2 hours after insulin and fluids were given.

Determinations of oxygen content of arterial and venous blood showed a narrow difference between the 2 specimens. Venous oxygen saturation was high in the presence of reduced bloodflow. In 5 cases the arteriovenous oxygen difference was 1.3 to 3.4 vol. % and the venous oxygen saturation ranged from 83.3% to 88.8%. Cases 6 and 7 had arteriovenous differences of 5.1 and 6.7 vol. % of oxygen and venous oxygen saturation of 63.8% and 64.2%. Case 8 showed an arteriovenous difference of 12.6 vol. % oxygen and a venous oxygen saturation of 45.2%. This patient had received insulin and intravenous fluids at the time these studies were made. Venous oxygen saturation fell while blood flow rose during treatment in nearly all cases.

Estimations of oxygen utilization can be calculated from arteriovenous oxygen difference (1 cc. oxygen per 100 cc. of blood) and bloodflow (expressed as cc. blood per 100 cc. of hand). These estimations cannot be taken as absolute values because bloodflow was measured in the hand and blood gas determinations were made on blood drawn from the femoral vessels of the leg. However, venous oxygen values of blood obtained from the antecubital vein of the arm immersed in the plethysmograph corresponded closely with femoral vein blood values in Case 4. Bloodflow in the hand may not be an exact index of bloodflow in other parts of the body but may mirror the direction of change.⁴ With these reservations in mind we have listed in Table 1 oxygen utilization (expressed as cc. oxygen per 100 cc. of hand per minute) and the mental state of the patients. These figures suggest that there is a marked reduction in oxygen utilization in untreated diabetic acidosis. The patients with most markedly decreased oxygen utilization were semiconscious or unconscious; those with less marked reductions were conscious. Treatment seemed to be accompanied by an increase in oxygen utilization.

Blood pressure was reduced in all patients on admission. The degree of reduction varied. The most seriously ill patients were unconscious and had the lowest blood pressures ranging from 50 to 96 mm. of mercury systolic over 30 to 70 mm. of mercury diastolic. The patients whose clinical condition was much better were conscious and had nearly normal blood pressures.

Initial determinations for serum proteins, hemoglobin and cell volume were elevated above recovery levels in all cases. These observations served to indicate the severity of the dehydration.

Serum protein concentrations decreased after the administration of parenteral fluids. In Cases 4, 5 and 6 proteins fell sharply during treatment and then increased somewhat during the recovery period. All of these patients received 6% acacia intravenously. Case 3 received acacia but failed to show any marked reduction of serum protein. The other cases showed a reduction of serum pro-

teins from the level on admission to that after hydration which was maintained after recovery.

Hemoglobin values fell during hydration. The levels after hydration were maintained. In Cases 4 and 5 the hemoglobin rose while the proteins fell during hydration. Both of these patients were seriously ill and both received acacia. Peters explained similar changes in his patients on the basis of continued loss of fluid containing protein. He found this in patients who were failing clinically. His patients did not receive acacia; ours did.

Cell volume by hematocrit paralleled the changes in hemoglobin.

All of these studies, except the peripheral bloodflow, were made on 11 additional patients with consistent results. These results were not included because oxygen capacity was calculated from hemoglobin values, the volumetric Van Slyke apparatus was used for the blood gas analyses and peripheral bloodflow was not measured. Although the number of cases reported is small, the findings are significant because of the consistency of the results in the 8 cases and the consistency of the group of 8 with the 11 preliminary cases.

Discussion. Our observations on the serum protein concentration, hemoglobin and cell volume by hematocrit in patients with diabetic acidosis agree with those of Peters *et al.*^{15,16} They point to a severe dehydration and hemoconcentration. These patients had long periods of hyperglycemia and glycosuria resulting in diuresis preceding the acidosis. Atchley and his coworkers³ found that withdrawal of insulin from diabetic patients produced an increase in the excretion of sodium, potassium and chloride with diuresis. This initial electrolyte loss occurred independently of the development of ketosis. They also found that after a longer period of insulin withdrawal there occurred an accumulation of ketone bodies which further depleted the stores of fixed base and when the alkali reserve depleted uncompensated acidosis developed.

Chang, Harrop and Schaub⁵ showed that the dehydration of diabetic acidosis was accompanied by a reduction in blood volume. The acidosis in their cases was less severe than that found in those we studied. All of their cases were sufficiently conscious to cooperate in measurement of blood volume by the carbon monoxide method. Although their patients had relatively mild acidosis, the reduction in blood volume varied from 250 to 600 cc. If patients with relatively mild diabetic acidosis show a reduction of blood volume up to 600 cc., it is not unreasonable to believe that our patients in severe diabetic acidosis with associated peripheral circulatory failure would have more marked reduction in blood volume.

Cold extremities, rapid, thready, low volume pulse and low blood pressure, well-known characteristics of surgical shock, were seen in the patients in diabetic acidosis with peripheral circulatory failure. Freeman *et al.*¹¹ found that patients in surgical shock had marked

reduction in peripheral bloodflow. Dogs in which shock had been produced experimentally^{8c,10} showed hemoconcentration, reduced blood volume and peripheral bloodflow. The increased hemoglobin, serum protein concentration and cell volume in our patients indicated the extent of the dehydration and hemoconcentration and suggested the probable existence of a reduced blood volume. Measurements of the bloodflow through the hand indicated the severity of reduction in the peripheral circulation. These observations indicate that our patients like those in surgical shock have peripheral circulatory failure. A suggested mechanism for the production of peripheral circulatory failure in diabetic acidosis is summarized in Figure 4. The vicious circle leading to peripheral circulatory failure has been adapted from Freeman's paper.^{8b}

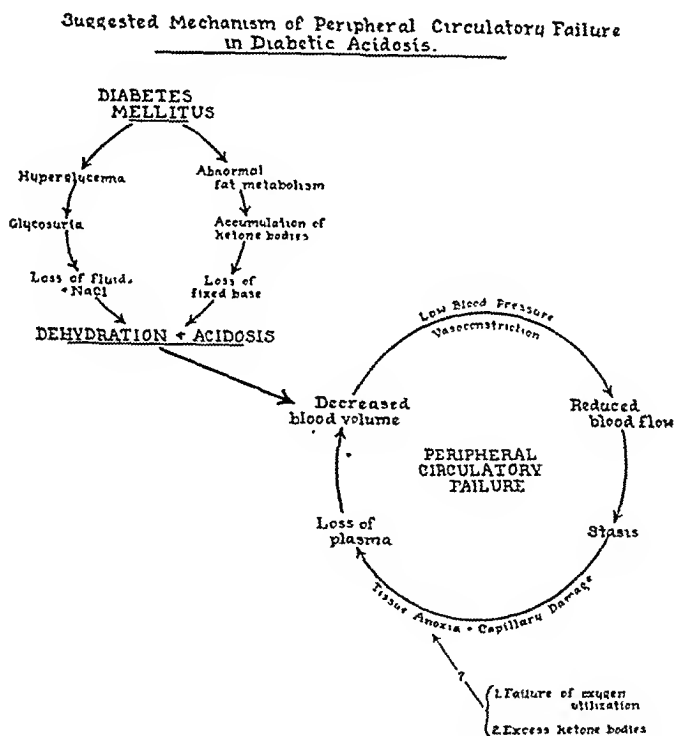


FIG. 4.—Suggested mechanism of peripheral circulatory failure in diabetic acidosis

Blood gas analyses in surgical shock¹¹ show a widening of the arteriovenous oxygen difference with a marked reduction in venous oxygen saturation. This reduced venous oxygen content is regarded as the result of reduced circulation; the tissues having obtained as much oxygen as possible from the blood delivered at a markedly reduced rate of speed. When the reduction in bloodflow is so great, that even very complete removal of oxygen from the blood arriving

fails to deliver an adequate oxygen supply per unit of time, tissue anoxia results. This is the stagnant type of anoxia of surgical shock.

Patients in diabetic acidosis, however, were found to differ from those in surgical shock with respect to the level of their venous oxygen saturation in the presence of markedly reduced bloodflows. Figure 5 compares the bloodflow, arterial and venous oxygen saturation in the patients with peripheral circulatory failure in diabetic

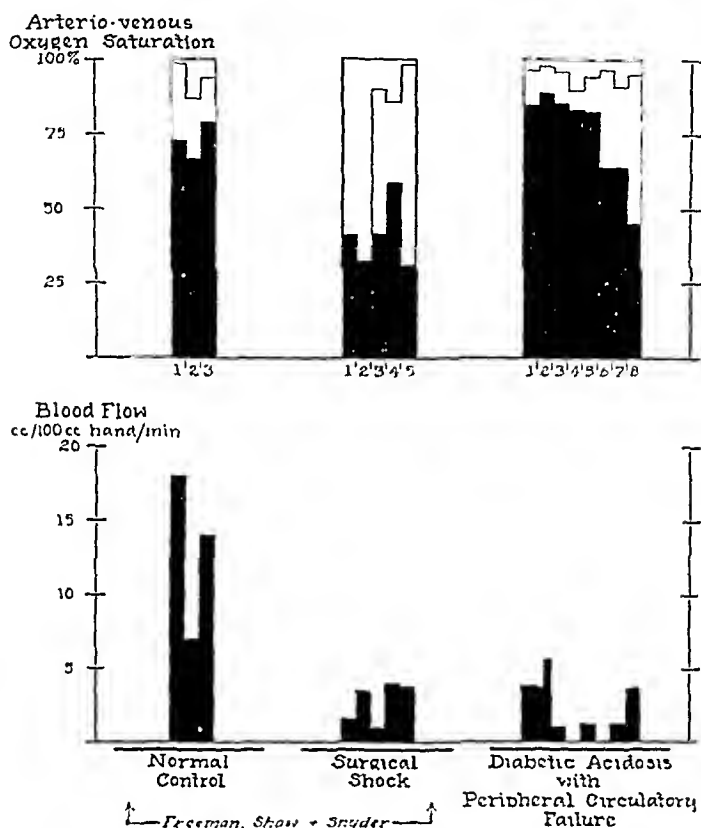


FIG. 5.—Comparison of bloodflow and venous oxygen saturation in diabetic acidosis with normal controls and surgical shock. Each column represents one case, as indicated by the numbers beneath the upper row.

acidosis with normal controls and patients in surgical shock studied by Freeman, Shaw and Snyder.¹¹ Reductions of peripheral bloodflow of the magnitude found in surgical shock were found in the patients with diabetic acidosis. Venous blood leaving such regions of reduced bloodflow, however, showed little oxygen unsaturation. The reduced peripheral bloodflow indicated the reduction in speed of arrival of hemoglobin bringing oxygen to the tissues. The high venous oxygen saturation suggests a failure of the hemoglobin to liberate its oxygen to the tissues or a failure of the tissues to remove the oxygen which does arrive. These findings point to the existence of a histotoxic as well as a stagnant anoxia in the peripheral circulatory failure of diabetic acidosis.

Conclusions concerning oxygen utilization in any one part of the body cannot be made with assurance unless the bloodflow and arteriovenous oxygen differences are measured in the same part. In these experiments bloodflow measurements were made on the hand, represent chiefly skin bloodflow and are not a measure of bloodflow in visceral organs. Venous blood gas analyses were made on blood drawn from the femoral vein. This blood consists of venous return from both superficial and deep leg tissues. However, evidence has been obtained suggesting that the estimated results of oxygen utilization obtained would not be altered greatly if blood gases and bloodflow had been measured in the same part. In Case 4, blood drawn from a superficial antecubital vein in the arm in the plethysmograph had a venous oxygen content very close to that obtained on femoral vein blood during acidosis and after recovery.

Results calculated from arteriovenous oxygen difference and bloodflow suggest that there is a decrease in the ability of the tissues of patients with untreated diabetic acidosis to utilize oxygen. The degree of reduction of oxygen utilization may be correlated with the mental state of the patient. Treatment is accompanied by an apparent increase in tissue oxygen utilization. The levels reached during treatment are greater than recovery levels and indicate possible repayment of an oxygen debt. Speculation concerning possible causes for a failure of oxygen utilization in diabetic acidosis centers around: 1, inability to utilize carbohydrate; 2, ketosis, or 3, acidosis. Any one, or all three, may be responsible for the findings.

The reduction in circulation which all of our patients showed in varying degrees was present before treatment was started and was an integral part rather than a late complication of the diabetic acidosis. When there was a moderately reduced peripheral bloodflow but with maintained blood pressure (Fig. 1) saline solution given by hypodermoclysis was sufficient to increase the bloodflow, to maintain the blood pressure and to correct the dehydration. It may be inferred that the blood volume was restored and maintained by this form of treatment alone.

When there was a more marked reduction in peripheral circulation, a low blood pressure and unconsciousness (Figs. 2 and 3), saline or other solutions of electrolytes without colloid osmotic pressure, when administered either by hypodermoclysis or by the intravenous route, seemed to be insufficient to bring about a permanent increase in bloodflow and blood pressure or to restore the blood volume. It seemed as though the reduced peripheral circulation did not absorb fluids given by hypodermoclysis. Again, it is probable that the vascular system in peripheral circulatory failure cannot retain osmotically inactive fluids. Finally, it is recognized that saline brings about a temporary increase but does not maintain

the blood volume (Freeman and Wallace⁹). For these patients in peripheral circulatory failure adequate volumes of osmotically active solutions such as plasma, blood or aëcia should be given early by the intravenous route and should be continued until bloodflow and blood pressure are increased and maintained. Saline given simultaneously or subsequently for the replacement of electrolytes and water will then probably be effectively absorbed and retained.

The results of these studies lead us to believe that the prompt restoration of blood volume is almost as important as the administration of insulin in the treatment of diabetic acidosis. Even though lack of insulin be the initiating factor in the series of events leading to the development of diabetic acidosis with peripheral circulatory failure, in treatment measures directed toward restoration of blood volume and adequate circulation should be instituted before or simultaneous with the administration of insulin.

Summary and Conclusions. 1. Eight patients with diabetic acidosis were studied. Initially elevated hemoglobin, hematocrit and serum protein with a decrease following administration of fluids showed the presence of dehydration and hemoconcentration.

2. Peripheral bloodflow in the hand, as measured by the plethysmograph was reduced.

3. Venous oxygen saturation was high in the presence of marked reductions in peripheral bloodflow.

4. Physiologic evidence presented supports the clinical impression of the existence of peripheral circulatory failure in diabetic acidosis.

5. The existence of an unusually high venous oxygen saturation in the presence of a reduced peripheral bloodflow suggests a failure of oxygen utilization by the tissues. Possible causes suggested for the failure of oxygen utilization are: 1, inability to utilize carbohydrate; 2, ketosis, or 3, acidosis.

6. These findings point to the existence of a histotoxic as well as a stagnant anoxia in the peripheral circulatory failure of diabetic acidosis.

7. The importance of the prompt restoration of blood volume and the maintenance of adequate circulation in the treatment of diabetic acidosis is stressed.

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THE RESULTS OF SULPHOCYANATE THERAPY IN HYPERTENSION.

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POTASSIUM sulphocyanate therapy was first employed in the Cardiology Department of the Wisconsin General Hospital in certain selected cases of hypertension in 1929. A much broader application of this type of treatment was made possible by Barker's announcement in 1934 of a method for determining the blood cyanates and this form of laboratory control has been used routinely since June, 1935. The experience in a group of 50 cases has been so satisfactory that it seemed advisable to report the results obtained in this series, particularly in view of the current controversy over the propriety of administering thiocyanate to patients with hypertension.

Barker's original publication^{1a} presenting his method of treating hypertension with potassium sulphocyanate contained a comprehensive review of the literature up to March, 1936. A few of the authors mentioned in his bibliography had been favorably impressed with the results of this drug but the majority of the writers were opposed to it on the grounds that the effective dosage was sufficiently toxic to produce unpleasant and sometimes dangerous side reactions. Barker, in his paper, presented a method of administering thiocyanate which was both effective and safe provided proper laboratory control was available. He described a relatively simple technique for the determination of the blood cyanate. His patients were given from 0.3 to 1 gm. of potassium sulphocyanate daily for

a number of days until the blood cyanate reached a level of from 8 to 10 mg. per 100 cc., at which time the dose was reduced to a point which would maintain the blood cyanate somewhere in the therapeutic range which was found to vary between 6 and 12 mg. per 100 cc. Of the 45 patients reported in his series, 35 obtained a distinct drop in the blood pressure and definite relief from their symptoms. It was pointed out that the toxic range lay well above 15 mg. and that serious complications and fatalities probably occurred only when the level reached 40 to 50 mg. Untoward symptoms were avoided by so regulating the dose as to maintain the blood cyanate well below the toxic level and within the therapeutic range. In January, 1937, Barker^{1b} published a second paper in which he reviewed and brought up to date the data presented in his original article. Later in that year Griffith, Lindauer and Campbell⁶ reported a series of 26 hypertensive patients treated with thiocyanate after the method of Barker. They encountered no fatalities and no major complications. Of 16 patients adequately treated and controlled, they obtained good results in 10. They presented a micro-modification of Barker's method for determining the blood cyanate using standards made of colored ink. This method required only a few drops of blood which could be obtained by puncturing the finger and avoided the necessity of drawing blood from a vein. Steidl and Steenken¹¹ administered potassium sulphocyanate to 3 patients with pulmonary tuberculosis and hypertension. A definite reduction in the blood pressure was obtained in all 3 cases and in none was there any evidence of deleterious effects so far as the tuberculosis was concerned. Massie, Ethridge and O'Hare⁸ gave sodium sulphocyanate to a series of 14 ambulatory hypertensive patients and made a special effort to eliminate as far as possible all psycho-therapeutic effects. The blood cyanate was maintained between 5 and 7 mg. per 100 cc., and a lowering of the blood pressure was obtained in every case. No changes in the renal function were noted, there was no tendency to develop anemia, the ophthalmoscopic findings showed no alteration and serial electrocardiograms, taken on a few of the patients, showed no deviation from the controls. A variety of untoward symptoms were noted, including skin eruptions, nausea, vomiting, diarrhea, mental confusion and precordial pain but no serious complications were encountered. These authors concluded that patients treated by this method should be carefully selected and closely observed, and that proper control of dosage was necessary in each individual case according to the cyanate level in the blood. More recently, Wald, Lindberg, and Barker¹² reviewed the toxic manifestations encountered in cyanate therapy. They admitted that the thiocyanates were toxic and stated that their beneficial action in reducing blood pressure depended to a certain extent on their peculiar toxicity. For the most part, the toxic symptoms were mild

when the blood cyanate was kept at a safe level and became severe only when the amount of cyanate in the blood became definitely elevated. No patient who had previously experienced angina pectoris suffered a greater degree of angina during potassium sulphocyanate therapy, although they felt certain that in a few cases angina had developed as a direct result of the hypotensive action of the drug. No alterations in the *electrocardiogram* were noted. Garvin⁴ reported a fatal case in which the toxic manifestations of the thiocyanate appeared while the blood level was supposedly in the non-toxic range and death was thought to be due to an idiosyncrasy to the drug. He concluded that since such intolerance cannot be recognized in advance, thiocyanate therapy must be considered dangerous. Robinson and O'Hare¹⁰ published the results of their experience with a series of 75 patients treated with thiocyanates which in general paralleled those of Barker. Mosenthal,⁹ in reviewing the medicinal treatment of hypertension, stated: "There is no doubt that the cyanates in sufficient doses will lower blood pressure and relieve symptoms of hypertension, though their administration is associated with considerable danger." But he added: "Control of the thiocyanate administration by quantitative determination of the cyanates in the blood, as suggested by Barker, is a distinct advance in this therapy. The original conclusion of Barker that the optimal therapeutic level ranges between 7 and 12 mg. per 100 cc. of blood and that higher concentrations may be associated with toxic manifestations has been verified and furnishes an excellent guide to the rational use of the cyanates."

Current Comment² has recently called attention to several unfavorable reports regarding the sulphocyanates, including the one by Garvin,⁴ and concluded: "The value of sodium or potassium thiocyanate, in the light of its dangerous possibilities, seems more doubtful than ever."

It is obvious from the controversial nature of the foregoing references that the advisability of administering thiocyanates for the control of hypertension is still a moot question. It can be settled only through further experience and by the reporting of results obtained by physicians dealing with this problem.

Present Series. During the past 11 years 50 patients consisting of 21 males and 29 females with "essential hypertension" have been treated with potassium sulphocyanate in the Cardiology Department of this hospital.* With one or 2 exceptions all were ambulatory throughout the period of observation. The important characteristics of the group have been summarized in Table 1. The age of the patients ranged from 16 to 78 years (average, 51). In the 39 cases in which hypertension had been diagnosed previous to their being seen in the Cardiology Department, the known duration

* We are indebted to Dr. M. J. Lustok of Milwaukee for the follow-up data on one of the patients who originally belonged to this series.

of the condition varied from 1 month to 25 years with a mean of 5 years. Evidence of hypertensive, rheumatic or coronary heart disease was found in 30 patients and signs of renal involvement were present in 19. Arteriosclerosis was relatively common. Other complications such as diabetes, glaucoma and food allergies occurred less frequently. The systolic blood pressure after a period of stabilization and prior to starting sulphocyanate therapy, ranged from 155 to 245 mm. of mercury with a mean of 197 for the entire group. The diastolic pressure ranged from 90 to 145 with a mean of 115.

TABLE 1.—PRESENT SERIES.

	Males.	Females.	Total.
Number of cases	21	29	50
Age in years:			
Range	16-65	38-78	16-78
Average	49	53	51
Known duration of hypertension in 39 cases:			
Range	3 mos.-13 yrs.	1 mo.-25 yrs.	1 mo.-25 yrs.
Average	4.3 yrs.	5.8 yrs.	5.1 yrs.
Number of cases treated under labor- atory control	18	25	43
Number of patients with heart disease	15	15	30
Number of patients with renal involve- ment	11	8	19

Method. In practically every case the patient was observed over a period of at least 3 months, and in many instances for one or more years, during which the usual hygienic measures were instituted and various types of treatment employed, including vasodilators, potassium iodide and sedatives such as bromides and barbiturates. Blood pressure readings were taken at frequent intervals and it was not until after the arterial tension had become relatively stabilized under this sort of a regimen that potassium sulphocyanate therapy was begun.

The drug was administered in an aqueous solution* containing 5 grains to the dram and the patient started on a dose of 1 dram (5 grains) 2 or 3 times a day. The blood cyanate was determined at weekly intervals and the initial dose continued until the therapeutic level of 6 to 12 mg. per 100 cc. was reached. The amount was then reduced and a maintenance dosage was determined for each individual patient such that the blood cyanate was kept within the therapeutic range at the level which appeared to produce the optimum blood pressure response. After the first few weeks, blood samples were taken at approximately monthly intervals, and in some cases even less frequently.

It should be emphasized that no attempt was made to force an excessively high blood pressure down to a normal level, but simply to reduce the tension below the danger range and thus relieve the excessive strain on the heart, kidneys and cerebral vessels.

Results. Subjective Improvement. The degree of subjective improvement is given in Table 2. Four of the patients had experienced none of the usual hypertensive symptoms but of the 46 who

* Recently some patients have been receiving enteric-coated tablets containing 3 grains of potassium sulphocyanate supplied through the courtesy of the Eli Lilly Company of Indianapolis. These have proved highly satisfactory and, for the most part, have been preferred by the patients.

complained of headaches, dizziness, tinnitus, easy fatigue and other distressing sensations commonly associated with hypertension, 13 (28%) reported practically complete relief from their symptoms and were rated as showing *excellent* subjective improvement. The results were considered *good* in 16 (35%), *fair* in 9 (20%), while relatively little or no improvement was noted in 6 (13%). Grouping the *excellent* and *good* results together, approximately 63% felt definitely better while taking cyanate. Six patients tolerated the drug poorly as evidenced by precordial pain in 1, a skin rash in 3 and a skin rash combined with falling hair in 2. One patient complained of nausea at first, but this was of short duration and did not prevent continuance of the treatment. The most serious toxic reaction encountered occurred in a woman of 68 who became mentally confused and went into a state of physical collapse in spite of the fact that the blood cyanate did not exceed the accepted therapeutic level. During the course of the next 3 years, two subsequent attempts were made to administer cyanate because of a dangerous and uncontrollable rise in the arterial tension, but a repetition of the toxic reaction on both occasions made it necessary to abandon this form of therapy. Another patient, a woman of 38, did not feel as well while taking the drug, and although the blood pressure response was fairly satisfactory, cyanate had to be discontinued.

TABLE 2.—DEGREE OF SUBJECTIVE IMPROVEMENT.

	No. of cases.	%.
Excellent	13	28
Good	16	35
Fair	9	20
Poor or none	6	13
Worse	2	4
Total	46*	100

* Four of the group of 50 patients experienced no hypertensive symptoms.

Objective Improvement. The results with respect to objective improvement are summarized in Table 3. The degree of improvement was judged largely on the drop in the blood pressure, although other factors such as reduction in the degree of cardiac dilatation and disappearance of congestive failure were also taken into consideration in grading the results. The response was considered *excellent* if a moderately high blood pressure could be controlled at or below 150 systolic and 90 diastolic. The results were judged as *good* if a systolic level of 160 to 170 and a diastolic level of 100 or slightly over could be maintained. Lesser responses were graded as fair or poor, depending upon the individual circumstances. Classification into these various grades was modified to a certain extent by the height of the original blood pressure level and the number of millimeters of mercury through which the pressure dropped. In one man, who, previous to treatment, had been carry-

ing a tension of 245/145, the reading fell to 180/110 with cyanate therapy and the result was considered *good*. In another patient whose pressure dropped from 190/115 to 175/110, the result was considered *poor*.

TABLE 3.—DEGREE OF OBJECTIVE IMPROVEMENT.

	No. of cases.	%.
Excellent	24	48
Good	15	30
Fair	8	16
Poor	3	6
Total	50	100

Referring to Table 3, it will be noted that objective improvement was considered excellent in 48% of the series, good in 30%, fair in 16% and poor in 6%. Some degree of reduction was obtained in every case, but satisfactory results, grouping the *excellent* and *good* responses together, were noted in 78%. In the remaining 22% the results were more or less disappointing, but in only 6% were they practically *nil*.

Blood Pressure Response. The actual drop in the blood pressure for the entire group will be found in Table 4. The level at which each patient stabilized during the preparatory period was noted and the range for the group as recorded under the heading "Before KCNS" was 155 to 245 systolic and 90 to 145 diastolic. The mean for the entire series was 197 systolic and 115 diastolic. The level at which the blood pressure could be maintained by adequate doses of cyanate was determined from a large number of readings in each case and the results for the group have been listed under the heading "With KCNS." The systolic pressure under treatment varied from 130 to 210 with an average of 156 and the diastolic varied from 70 to 130 with an average of 94. This represents an average drop of 41 mm. of mercury in the systolic pressure and 21 mm. in the diastolic pressure.

TABLE 4.—EFFECT OF POTASSIUM SULPHOCYANATE ON THE BLOOD PRESSURE.

	Before KCNS.	With KCNS.	Net change.
Systolic B.P. in mm. Hg:			
Range	155-245	130-210	
Average for group	197	156	-41
Diastolic B.P. in mm. Hg:			
Range	90-145	70-130	
Average for group	115	94	-21

In most instances the blood pressure remained lowered only as long as the blood cyanate was maintained at a certain minimum level, but in 4 patients who had been known to have hypertension for 1 to 2½ years, and in 1 where the previous duration was unknown, the blood pressure remained within the normal range for months

or years after the cyanate was discontinued. However, one is not warranted in holding out cyanate therapy as a possible "cure" for hypertension as such results have been decidedly the exception rather than the rule.

Optimum Blood Cyanate and Maintenance Dosage. As noted by Barker,^{1a} the therapeutic range for the blood cyanate seemed to lie between 6 and 12 mg. per 100 cc. although in rare instances good results were obtained with the blood cyanate as low as 4 mg. and in 4 cases levels of 13 to 16 mg. were necessary to obtain a significant lowering. Judged on the basis of the combined subjective and objective response the optimum blood cyanate level was estimated for each patient and the mean for the entire group was found to be 8.3 mg. per 100 cc.

Rather marked variation was noted in the dosage of potassium sulphocyanate needed to maintain the blood cyanate at the desired level in the individual case. A few patients required as little as 3 or 4 5-grain doses per week while others were found to need as many as 14. In one instance the requisite maintenance amount was 21 5-grain doses a week. Ten doses per week was found to be adequate for over a third of the patients and the average for the entire series was 9.

Blood counts, urinalyses and electrocardiograms showed no significant changes during the course of cyanate therapy. Serial orthodiagrams revealed a distinct tendency of the frontal area of the cardiac shadow to decrease as the blood pressure dropped. Results of this phase of the study will be reported in detail in a future communication.

Sympathectomy. Two patients were subjected to bilateral thoracic sympathectomy after having been given thorough trials of cyanate therapy. The first patient, a man of 51, whose blood pressure was 200/120 before commencing treatment, was controlled for a time at a level of 165 to 180 systolic and 105 to 110 diastolic, but in April, 1939, it became necessary to reduce the dose of thiocyanate due to the appearance of a skin rash, and the tension returned promptly to its previous level. In view of the fact that the response to treatment had not been satisfactory and that full doses of potassium sulphocyanate were no longer tolerated, sympathectomy was advised. On May 24, 1939, bilateral supra-diaphragmatic sympathectomy was performed by Dr. Loyal Davis of Chicago and for a few days thereafter the blood pressure was 120/72. During the next 2 or 3 weeks the tension gradually climbed to 180/110 at which the potassium sulphocyanate was resumed. The blood pressure promptly dropped to 150/100 where it remained for 5 months. At this time the patient's wife developed cancer and under the resulting nervous strain, the systolic pressure ranged from 170 to 180 and the diastolic from 100 to 110. After successful surgical removal of the wife's cancer, the patient's blood pressure

has again come under control in the neighborhood of 150/100, he has been entirely symptom-free, and the skin rash has not recurred.

The second patient, a nurse of 42 years, had been taking potassium sulphocyanate with good results for 2 years but then developed a skin rash. Sympathectomy was advised in the hope that even if the operation failed to effect a permanent reduction in the blood pressure, smaller doses of thiocyanate might be employed successfully afterward without the production of a dermatitis. Extensive sympathectomy was performed on September 5, 1940, and for several days thereafter the blood pressure remained around 130/80. About 3 months later the patient returned to active nursing duty and has been working ever since. At the present time, 7 months after operation, she feels better than she has in years, the blood pressure remains at a relatively normal level and there has been no indication for the resumption of cyanate to date. It is recognized, however, that more time will have to elapse before the actual results of the sympathectomy can be accurately evaluated in this case.

Mortality. During the 11 years covered by this study, 4 patients in the series died of congestive heart failure, 4 of cerebral hemorrhage, 1 of coronary occlusion and 2 of pneumonia. In no instance could death be attributed in any way to the thiocyanate. In fact, none of the 9 patients who died of their cardiovascular disease had been taking cyanate for 1 or more months preceding death. One man of 43 who had shown an excellent response to cyanate therapy felt so well that he discontinued treatment of his own accord. One month later the blood pressure rose to 170/130 and a fatal cerebral hemorrhage occurred. A banker, 45 years of age, who was fairly well controlled over a period of 8 months on potassium sulphocyanate voluntarily discontinued the drug during the fall of 1937 and in January, 1938, suffered a subarachnoid hemorrhage which incapacitated him for several weeks. He was readily persuaded to resume cyanate therapy after he had recovered and was faithful to the treatment for about 9 months. At this time he decided to discontinue cyanate and give a garlic and parsley preparation a trial. He did not again return for observation and about 1 year later was reported to have died of a cerebral hemorrhage. Judging from the mortality experience furnished by this limited series, it would appear that a hypertensive patient is actually safer while taking cyanate in adequate doses, for in no instance did a patient die while taking the drug. Moreover, in only one instance did a cerebral hemorrhage occur while a patient was taking cyanate and this happened in one of the few patients whose blood pressure responded very poorly to treatment. Obviously, it is impossible to draw any definite conclusions as to the ability of cyanate therapy to prolong the life of a hypertensive patient as there is no way of knowing how long the patient would have lived without treatment; but the

authors have obtained the clinical impression that cyanate does postpone heart failure and cerebral accidents and thus tends to prolong life in those patients who respond well to therapy.

Case Reports. CASE 1.—J. M., a 55-year-old white male, was first seen in the Cardiology Department, October 9, 1936. He had been known to have high blood pressure for the past 11 years and, during this period, had experienced temporal and occipital headaches which usually came on right after breakfast and lasted all day. They had occurred only infrequently for several years but recently had been present every day and were becoming almost unbearable.

On physical examination the pulse was regular at the rate of 72 and the blood pressure was 210/110. Systolic murmurs were present at the mitral and aortic areas. There was no evidence of congestive failure.

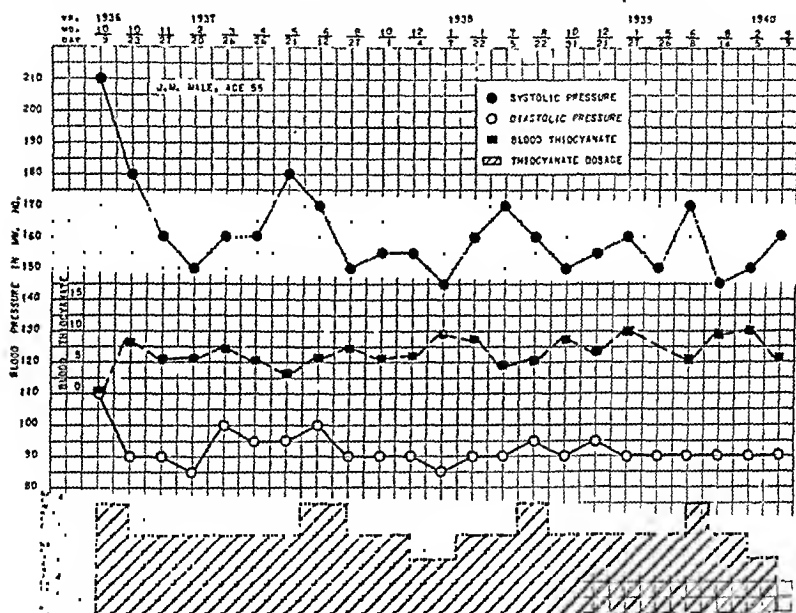


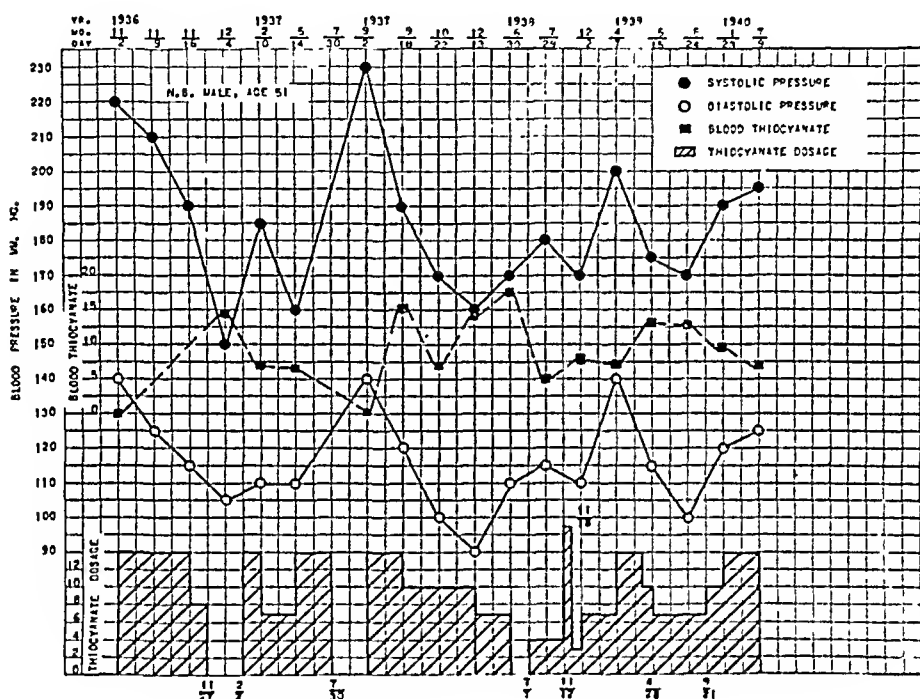
CHART 1.—Clinical course in Case 1, a 55-year-old white male. Had suffered from hypertension and severe headaches for 11 years. Symptoms were completely controlled by thiocyanate therapy. Chart covers a period of 4 years and is composed of representative readings obtained at intervals. The thiocyanate dosage is graphed as number of 5-grain doses per week.

Orthodiascopic examination revealed moderate dilatation of the aorta and moderate enlargement of the left ventricle. The electrocardiogram showed the typical pattern of left ventricular strain.

The following diagnosis was made: hypertensive heart disease, moderate cardiac enlargement, moderate dilatation of the aorta, advanced myocardial degeneration, marked hypertension, relative mitral regurgitation and diabetes mellitus.

Since the patient was known to have had hypertension for at least 11 years and in spite of various types of treatment had continued to suffer from severe headaches, he was immediately started on potassium sulphocyanate and was given 5 grains twice daily for 2 weeks after which he was maintained on a dose of 5 grains 10 times weekly. The headaches com-

pletely disappeared after 3 weeks and did not recur for a period of 2 years. During the past 2 years there has been a tendency for the headaches to return although they have not been nearly as severe nor as frequent as previously. Strangely enough the recurrence of the headaches has not been accompanied by a rise in blood pressure. This patient's course is shown graphically in Chart 1 and it will be seen that his systolic pressure has been maintained at an average of 160 and the diastolic in the neighborhood of 90. The blood cyanate has ranged for the most part between 5 and 10 mg. per 100 cc. This man has remained ambulatory and serial orthodiagrams have shown no increase in the heart size. In February, 1940, he went through an attack of lobar pneumonia from which he made an uneventful recovery. The cardiac reserve has remained low but there has never been any evidence of frank congestive failure.



Orthodiascopic examination confirmed the clinical impression of moderate cardiac enlargement. The electrocardiogram showed the characteristic pattern of left ventricular strain with depression of the character and inversion of the *T* waves in Leads I and II.

A diagnosis was made of hypertensive heart disease, moderate cardiac enlargement, marked hypertension, congestive failure, functional capacity IV. Since he had been at complete rest for the past 3 weeks with very little improvement, he was immediately started on potassium sulphocyanate and given 5 grains twice daily. This dose was continued for 2 weeks at which time the blood cyanate had reached 14 mg. per 100 cc. and the blood pressure had dropped to 190/115. The patient improved rapidly both subjectively and objectively and by maintaining the blood cyanate at a level of 12 to 15 mg. it has been possible to keep the systolic pressure between 160 and 180 and the diastolic pressure between 105 and 110. After a few weeks, the gallop rhythm and the pulsus alternans disappeared, the patient went back to work and has been putting in a full day at his store ever since. He has never had a recurrence of the paroxysmal dyspnea during the 4 years and subjectively has felt as well as ever. On one occasion he discontinued the potassium sulphocyanate of his own accord for about a month and the blood pressure rose to 230/140. Resumption of the cyanate promptly restored the blood pressure to its former level (see Chart 2).

This man still runs a moderate hypertension but the blood pressure has been kept out of the danger range for a period of 4 years during which time he has been practically free from symptoms and has been able to carry on his business. There is no doubt in the minds of the various physicians who observed him in 1936 that he would have died in a short time had not the blood pressure been brought under control. It seems fair to assume that through the agency of potassium sulphocyanate, this patient has been given at least 4 additional years of life during which he has been free from discomfort and able to support his family.

CASE 3.—A. H., a woman of 48, employed as an office secretary, was referred to the Cardiology Department May 17, 1933. Hypertension had been discovered 3 years previously and she had been suffering from frequent severe vertical headaches coming on during the night or early morning and lasting most of the day. The systolic pressure had ranged from 150 to 180 and the diastolic from 100 to 120.

The family history was significant in that the mother and father had both died of cerebral hemorrhage and 1 brother and 1 sister were known to have hypertension. (Both the brother and sister, neither of whom were treated with cyanate, have since died of "strokes" while patient has been under observation.)

On physical examination the pulse was regular at a rate of 86 and the blood pressure varied from 185 to 200 systolic and from 120 to 130 diastolic. The heart was slightly enlarged and the aortic second sound had a "bottom-of-the-well" quality. There was no evidence of congestive failure. Orthodiascopic examination revealed slight dilatation of the aorta and moderate cardiac enlargement. The electrocardiogram was normal except for a deep *Q* wave in Lead III.

Barker's method of laboratory control was not available at this time and the patient was given 2 grains of potassium sulphocyanate 3 times daily for 2 weeks during which the blood pressure dropped to 130/90 and the headaches completely disappeared. During the next 3 years the patient continued to take this dose of potassium sulphocyanate for 2-week periods with intervals of several weeks between courses. Since July 31, 1936, she has taken a maintenance dose of 5 grains of this drug 10 times weekly which has kept the blood cyanate in the neighborhood of 5 to 6 mg. per

100 cc. and has controlled the blood pressure at an average level of 135/90. She has been entirely free from headaches during this time. In October, 1938, the blood pressure was 125/80 and the drug was discontinued temporarily. Six weeks later the blood pressure was found to be 160/105 but the headaches had not returned. The cyanate was resumed and the blood pressure has been controlled in the region of 140/95 ever since. The clinical course is illustrated in Chart 3.

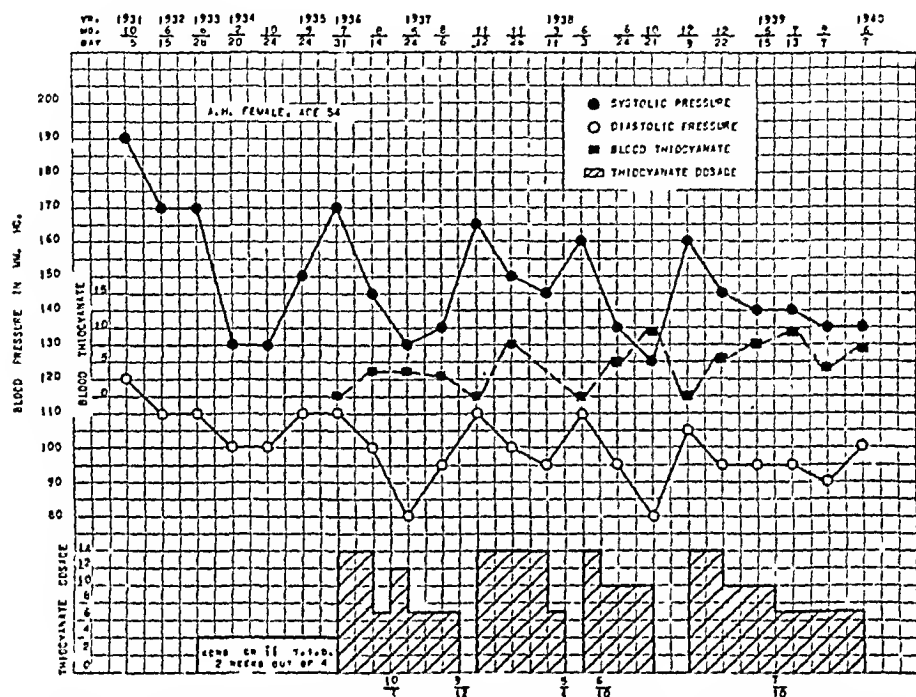


CHART 3.—Clinical course in Case 3, a 54-year-old white female. Patient has been under treatment with thiocyanate for 9 years. Blood pressure has been satisfactorily controlled on 7 to 10 5-grain doses per week.

Discussion. Notwithstanding the monumental experiments of Goldblatt,⁵ dealing with the production of hypertension in dogs and the numerous elaborate studies which have been inspired by his work, the problem of the etiology and mechanism of "essential hypertension" in man is still not clearly understood. As a result there is a great diversity of opinion among leading authorities as to whether one is ever justified in attempting to reduce an elevated blood pressure. Those who take the negative side of the question oppose treatment on the grounds that hypertension is a compensatory mechanism necessitated by a pathologic reduction in circulation to some tissue or organ and that a lowering of the arterial tension will result in a deficient blood supply to the tissue or organ involved. On the other hand, many eminent clinicians feel that an excessively high blood pressure, uncontrolled over a period of years, in most instances leads to heart failure, cerebral hemorrhage or uremia and premature death, and that if a moderate reduction of the blood pressure can be effected, the degenerative process can be retarded

and life prolonged possibly for a number of years. To those who believe in actively treating and reducing an elevated blood pressure, potassium thiocyanate offers an effective weapon which can be depended upon to afford both subjective and objective relief in the majority of cases.

It must be remembered that thiocyanate is a toxic drug and cannot be employed indiscriminately. It should never be given unless laboratory control is available and both doctor and patient are willing to take the trouble of having the blood cyanate checked at regular intervals. The individual variation in the susceptibility and response of patients is so marked that the optimum blood cyanate level and the dosage necessary to maintain this level have to be determined for each case. Treatment should not be offered to any patient who is not willing to coöperate fully and report for blood cyanate determinations at frequent intervals until his optimum dose has been determined. Except in rare instances the margin of safety between the therapeutic and toxic range is sufficiently wide to enable one to easily avoid any serious reactions due to the drug itself if reasonable care is exercised. Minor complications such as skin rashes, falling hair and mild aching of the muscles, particularly those of the thigh, may be expected in approximately 10% of the cases, but only infrequently will it be necessary to discontinue treatment permanently. Organic heart disease and even fairly marked degrees of renal impairment have not proved to constitute contraindications to the drug. However, it has been found that patients who have suffered a cerebral accident do not respond well to this type of therapy.

We feel compelled to take issue with the conclusions expressed in a paragraph entitled, "Hypertension and the Thiocyanates" (in Current Comment of the *J. Am. Med. Assn.*²). Referring to Garvin's paper⁴ the statement was made that, "A recent communication revealed eight fatalities reported as following the intake of thiocyanate." An analysis of Garvin's paper shows that of 7 fatal cases collected from the literature, 3 of the patients were not under treatment with the drug but took large amounts with suicidal intent. It is hardly fair to include such cases as an argument against the therapeutic use of a drug. In the case which Garvin himself reported, cyanate intoxication could probably have been avoided had the principles and methods advocated by Barker been more closely followed. Terminally, there was clinical evidence of bronchopneumonia which was confirmed at autopsy. It is perfectly possible that the pulmonary infection rather than the cyanate intoxication may have been the actual cause of death.

Current Comment² also stressed the findings of Hamilton *et al.*,¹ who had observed the effect of sodium thiocyanate on the blood pressure of hypertensive dogs. These investigators had observed a definite fall in pressure following administration of this drug, but

attributed the results to weather changes, and concluded that, "Cyanate did not produce a significant permanent lowering of the blood pressure in hypertensive dogs." Unfortunately, the crucial figures were lacking from their published data and the conclusions drawn were not warranted by the material presented. We strongly question whether Current Comment, on the basis of the material on which it predicated its opinion, can justify the implication that thiocyanate is too dangerous a drug to use clinically and possibly should be abandoned. No one will deny that the sulphocyanates are more or less toxic, but if the dose is intelligently regulated through adequate laboratory control as previously described, therapy can be extremely valuable and relatively safe.

The present outlook for combined sympathectomy and cyanate therapy is somewhat promising for those cases which do not respond to cyanate alone, but considerably more time and experience will be required to determine the value of this rather radical procedure.

Summary and Conclusions. During the past 11 years 50 patients with essential hypertension have been treated by the authors with potassium sulphocyanate. Barker's method of laboratory control has been employed routinely since June, 1935.

Subjective improvement as estimated by the disappearance of headaches, dizziness, tinnitus, and so on, was very definite in 63%, fair in 20% and disappointing in 17%. Six patients exhibited poor tolerance for cyanate as evidenced by precordial pain in 1, skin rash in 3 and skin rash combined with falling hair in 2. In addition, there were 2 other patients who felt distinctly worse while under treatment. One of these was apparently very sensitive to thiocyanate and treatment had to be abandoned because of mental confusion and physical collapse even with the blood cyanate in the accepted therapeutic range.

Some degree of reduction of the blood pressure was obtained in every case and objective results were considered satisfactory in 78%, fair in 16% and poor in 6%. The average systolic pressure for the entire group dropped from 197 before treatment to 156 with treatment while the average diastolic pressure dropped from 115 to 94. In 4 instances the blood pressure remained normal for months or years after discontinuing thiocyanate.

The optimum blood cyanate level ranged from 4 to 16 mg. per 100 cc. with an average of 8.3 mg. The maintenance dose of potassium sulphocyanate varied from 3 to 21 5-grain doses per week, with an average of 9 doses per week.

Extensive sympathectomy was performed in 2 cases but insufficient time has elapsed to properly evaluate the results.

During the 11-year period of observation 4 patients died of heart failure, 4 of cerebral hemorrhage, 1 of coronary occlusion and 2 of pneumonia. In no instance could death be attributed either directly or indirectly to cyanate administration.

Three illustrative cases have been described briefly.

Potassium sulphocyanate is regarded by the authors as a valuable drug in the treatment of hypertension and, properly employed, capable of prolonging life and relieving disability in a substantial percentage of patients suffering from this condition.

Potassium sulphocyanate can be safely administered provided proper laboratory control is exercised at all times.

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CONGENITAL HEART DISEASE DURING PREGNANCY.

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CONGENITAL heart disease constitutes between 1% and 2% of all organic heart disease so that it is a rare finding in pregnant women. Abbott's grouping¹ of these cases according to their tendency to cyanosis is of great importance because it affords a basis for predicting certain physiologic reactions under strain. This is particularly important when one wishes to arrive at a prognosis as to the effects of pregnancy and labor. Abbott's three groups are as follows: 1, the acyanotic group, those without abnormal communications between the right and left side of the heart; 2, the *cyanose tardive* group, those with an arteriovenous connection with the possibility of transient or terminal flow from the venous to the arterial side; 3, the *Morbus Caruleus* group with a permanent veno-arterial shunting of the blood. Diagnosis of the particular lesion present is notoriously difficult but the recent advances in diagnosis by means of Roentgen rays and the determination of the circulation rate from vein to lungs and from vein to periphery should be of definite assistance.

In 1905 Pouliot²⁰ stated that marriage was contraindicated in congenital heart disease only in the presence of cyanosis, and in 1912 Couderc⁶ concluded that if the condition was compatible with adult life, the prognosis depended less upon the form of the lesion than upon the state of compensation, degree of cyanosis and polycythemia, parity, and advent of complications especially tuberculosis and endocarditis. In 1920 Hochsinger¹⁰ emphasized the importance of preëxisting or developing cyanosis as an indication for the interruption of pregnancy, but more recently Shapiro and Simons²⁴ have stated that congenital heart disease even though accompanied by a high grade of cyanosis is not in itself a contraindication to pregnancy. Breed and White³ state, "If a patient with congenital heart disease has survived to the childbearing age without signs of incapacity for normal activity she will certainly be able to pass through pregnancy and labor without difficulty." Carr and Hamilton⁵ concluded that cases without communication between right and left sides of the heart or between the aorta and pulmonary artery did well, whereas those in which the possibility of venoarterial shunt existed sometimes developed sudden alarming symptoms as a result of the pressure changes which follow sudden emptying of the uterus. These symptoms most commonly developed after Cesarean section or internal podalic version and in some instances death had followed. The authors advocated postpartum binding of the limbs and abdomen to increase and maintain peripheral resistance.

In view of the varying opinions expressed by these different authors, it seemed important again to review a group of patients with congenital heart disease since there have only been sporadic case reports since the series collected by Couderc in 1912. Since 1932 at the New York Lying-In Hospital there have been 1089 recognized cases of organic heart disease in approximately 31,000 obstetrical patients. Of these 1089 cases, 20 (1.89%) have been diagnosed as having congenital heart disease and are summarized in Table 1.

There were 8 cases diagnosed as pulmonic stenosis, their average age being 24 and the average parity 0.5. It is not without some hesitation that we present a clinical group with this as the primary diagnosis but it was the sole discharge diagnosis in each instance. The cases, however, presented a common clinical picture indicating a congenital lesion which differed from the other diagnostic groups. All had a loud systolic murmur and most of them a thrill over the pulmonic area. There were varying degrees of enlargement of the heart and of the pulmonary conus. It is probable that other lesions also were present and possibly the tetralogy of Fallot in most of them, with its association of pulmonic stenosis, dextroposition of the aorta, patent interventricular septum and right ventricular hypertrophy. This is particularly likely to be the case in the

TABLE 1.—DATA ON 20 PREGNANT WOMEN HAVING CONGENITAL HEART DISEASE.

Case.	Diagnosis and functional class.	Age.	Parity.	Gravidity.	Cyanosis.	Electrocardiogram.	Röntgen ray and fluoroscopy of heart.	Duration of labor, hrs.	Blood loss, cc.	Comment.
1. J.H.	Pulmonic stenosis Class 2	23	0	1	0	RAD	Mod. enlargement, prominent pul. conus	10	100	Dysp. on exertion since infancy. Systolic thrill and murmur over pulmonic area. Mild clubbing. Nor. preg., labor, and puerperium.
2. M.R.	Pulmonic stenosis Class 2	25	1	2	Sl.	RAD	Markedly enlarged pul. conus. No gen. enlargement	(a) 36* (b) 21	100 500	Dysp. on exertion since childhood. Syst. thrill and murmur over pul. area. No clubbing. Cyanosis and orthopnea in both preg. Labors nor.
3. A.A.	Pulmonic stenosis Class 2	24	1	2	0	Neg.	Sl. enlargement l. aur. large pul. conus	21	140	Dysp. on exertion since childhood. Syst. thrill and murmur over pul. area. No clubbing. Cyanosis and orthopnea in both preg.
4. M.S.	Pulmonic stenosis Class 2	32	1	4	Sl.	RAD	Marked enlargement, prominent pul. conus	(a) 5 (d) 5	40	Dysp. on exertion since childhood. Syst. thrill and murmur over pul. area. Syst. murmur at apex. No clubbing. Cyanosis during latter part of preg. Nor. labor and puerperium.
5. V.P.	Pulmonic stenosis Class 1	19	1	4	0	RAD	Sl. enlargement, prominent pul. conus	(a) 7 (d) 7	50	No history of card. disease. Syst. thrill and murmur over pul. area. No clubbing. Nor. preg., labor, and puerperium.
6. M.P.	Pulmonic stenosis Class 2	25	0	1	Sl.	RAD	Mod. enlargement, prominent pul. conus	4	70	Known heart dis. since birth. Severe hypert. since 15 and one episode of renal failure at 21. Syst. murmur and ineffectual thrill at pul. area. Edema of eye grounds. No clubbing. Therap. abortion at 3 mos.
7. E.J.	Pulmonic stenosis Class 2	22	0	1	0	Neg.	Prominent pul. conus; nor. sized heart	Known heart dis. since birth with cyanosis and dysp. on exertion. No clubbing. Preg. at 19; therap. abortion 3 mos. Preg. at 22. Spontaneous labor, low forceps delivery at term.
8. D.T.	Pulmonic stenosis Class 3	22	0	2	Mod.	RAD	Marked enlargement; prominent pul. conus	6	50	Dysp. on exertion since childhood. Syst. thrill and murmur 3d and 4th interspace to left of sternum. No clubbing. Dysp., orthopnea, and palpitation latter part preg. Labor and puerperium nor.
9. C.S.	Interventricular septal defect Class 3	30	2	4	0	LAD	Mod. enlargement			

		Interventricular Septal defect			LAD	Sl. enlargement	(a) (b) (c) (d)	200	
		Class 2	Class 2	Class 1					
11. P.P.		26	0	1	0	Neg.	11	50	Known heart dis. and dysp. since childhood. Syst. apical thrill and murmur. No clubbing. Nor. preg., labor, and puerperium.
12. C.G.		26	1	3	0	Neg.	Known heart dis. since childhood. Syst. apical thrill and murmur. Mild clubbing. Nor. preg., labor, and puerperium.
13. R.P.		26	0	1	Sl.	LAD	No known hist. of heart dis. Apical syst. thrill and murmur. No clubbing. Nor. preg., labor, and puerperium.
14. E.B.		23	0	1	Sl.	LAD	Dysp. and palpitation for 6 yrs. Collat. circulation present. Apical and basal syst. murmurs. Feble peripheral pulsations, tremities. Abnor. in. in card. output. Elective Cesarean sect. at term. Normal puerperium.
15. R.Z.		27	0	1	0	LAD	4	20	Known heart dis. since childhood with dysp. on exertion. No trans. down aorta. Syst. thrill at base. Bl. press. RA 135/80, LA 130/60, RL 110/80, LL 100/80. Increased dysp. during preg., nor. labor, undue weakness during puerperium and develop. of diastolic murmur at base. Gen. cond. worse.
16. A.S.		21	0	1	0	LAD	Past hist. entirely neg. Collat. circulation present. Syst. murmur over entire precordium trans. down aorta. Bl. press. RA 135/80, LA 200/100, LA 230/110, RL 125/110, LL 125/110. First seen at 4th mo. of preg. Cesarean sect. and tubal sterilization at term after prelim. digital. Course satisfactory.
17. H.G.		20	1	2	0	LAD	7	20	No past hist. of card. dis. To and fro basal murmur. No clubbing. Nor. preg., labor, and puerperium.
18. G.B.		45	3	3	0	LAD	(a) 22 (b) 8	80	Dysp. on exertion since childhood. Syst. thrill and to and fro labors, or puerperia. No difficulty during either labors, or puerperia.
19. M.M.		25	0	2	0	LAD	(b) 48 (c) 24 (d) 18 (e) 16	50	Known heart dis. since childhood. Loud syst. murmur 3d left interspace. Slight clubbing. No difficulty during pregnancies, or puerperium.
20. L.W.		20	0	1	0	Neg.	Spontaneous abortion at 18 wks. Past hist. neg. except for known murmur since childhood. Loud syst. murmur over entire precordium. No clubbing.

* Letters refer to pregnancy for which information was available.

4 patients with cyanosis. As the authors had not personally seen all these patients it seemed better to treat them as a group in spite of the fact that some were more definitely suggestive of the tetralogy than others. Another reason for this decision is the frequency of the diagnosis of pulmonic stenosis in reports in the obstetrical literature so that this group is comparable with these cases.

Therapeutic abortion was performed in 2 instances. The first patient, Case 7, was a 22-year-old white primigravida with known congenital heart disease since birth. At the age of 15 she developed severe hypertension which was associated with headaches, dizziness, and marked dyspnea on exertion. At 21 she had an episode of renal failure. When first seen in the early part of pregnancy there was bilateral retinal edema. Cardiac examination revealed a loud systolic murmur and an inconstant thrill over the pulmonic area. Cyanosis and clubbing were absent. Blood pressure was 210/130. A roentgenogram of the chest revealed an enlarged pulmonary conus without appreciable cardiac enlargement. The electrocardiogram was negative. The vital capacity was 2000 cc. Blood chemistry and renal function tests were normal. Therapeutic abortion was performed under local anesthesia at 3 months' gestation primarily because of the hypertension and the past history of renal failure.

The second patient, Case 8, colored, aged 19 years, was also known to have had congenital heart disease since the time of birth, cyanosis and marked dyspnea on exertion having been present frequently. There was marked cardiac enlargement, a systolic murmur and thrill at the pulmonic area, and a systolic murmur at the apex. There were no pulmonary râles, edema or liver enlargement. The vital capacity was 1500 cc. Clubbing and polycythemia were absent. The electrocardiogram revealed right axis deviation. Cardiac films revealed enlargement of all chambers and fullness of the pulmonary conus. Because of the marked cardiac enlargement and the low cardiac reserve a therapeutic abortion was performed under open drop ether at 3 months' gestation. The patient was discharged in a satisfactory condition. She was seen again 3 years later when she appeared at the clinic 5 months pregnant suffering from lobar pneumonia and mild cardiac failure. She was digitalized and received 44 gm. of sulfathiazole over a period of 8 days. She recovered from the pneumonia. At this time Roentgen ray study, electrocardiograms and clinical examination failed to reveal any significant changes since the previous admission. In view of the advanced stage of the pregnancy the patient was kept on restricted activity in the hospital under digitalis therapy until delivery. She went into spontaneous labor at term and was delivered by low forceps at full cervical dilatation under local anesthesia. Throughout labor the pulse and respirations did not rise significantly, the maximum pulse rate being 96 and the maximum respiratory rate 22. The postpartum course was uneventful.

In this group of patients cardiac enlargement was present in 6. Mild cyanosis was present in 4 cases without increased intensity being noted during pregnancy or labor, and none had polycythemia. Three patients (Cases 2, 6 and 8) of the 4 who were cyanotic, complained of dyspnea on exertion which began about the fourth month of gestation, increased as pregnancy progressed but never became more than moderate in degree. The Functional Capacity (according to the scheme of the New York Heart Association) was diagnosed Class 2 in 2 cases, Class 3 in the other. Neither in these 3 cases nor in any other of the pulmonic stenosis group did the respirations rise above 24 per minute during labor. The fourth cyanotic patient suffered from dyspnea and palpitation throughout pregnancy with relief shortly after delivery. Neither this patient nor any other of the pulmonic stenosis group had a pulse rise over 110 per minute during pregnancy or labor. To summarize then, except for the 2 cases which required therapeutic abortion and the 1 patient who was successfully treated for pneumonia, this group presented no serious problems during pregnancy, labor or the puerperium.

Including the series of Coudere,⁶ Naish,¹⁶ and Jensen¹¹ there are 25 other reported cases of pulmonic stenosis complicating pregnancy. Jensen found the average age to be 22.9 and the average parity 1.5. There are no deaths which could be attributed to the lesion. Three patients had symptoms of cardiac insufficiency during pregnancy (Durozier,⁸ Laënnec,¹³ and Sireday,²⁵ the last case being complicated by patent foramen ovale), 2 patients had cardiac difficulty during labor (Courdec, Case 7, and Payraud,¹⁷ the latter case being complicated by an interventricular septal defect).

In the present series there were 4 cases of interventricular septal defect the average age being 28 and the average parity 1.3. None had cyanosis or polycythemia. Three had cardiac enlargement and 1 complained of dyspnea and palpitation on exertion beginning about the fourth month of gestation, increasing as pregnancy progressed so that she was diagnosed as Class 3 Functional Capacity. There was some relief of the dyspnea at term prior to labor. In this case labor was uneventful, the pulse and respirations remaining at physiologic levels, and all symptoms disappeared within the first 24 hours postpartum. In summary, this group presented no serious problems during pregnancy, labor, or the puerperium.

Including the series of Coudere and Jensen there are 32 other reported cases of interventricular septal defect complicating pregnancy. Jensen found the average age to be 28.5 and the average parity 2.2. Two of the 4 recorded deaths can be attributed to the lesion—both died of congestive failure at 6 months' gestation (Ferraro,⁹ and Jönen,¹² the latter case being complicated by a widely patent foramen ovale). Two patients had less serious cardiac difficulty during pregnancy (Bernard,² and Delsudre⁷), but there is no mention of difficulty during labor or the puerperium.

In the present series there were 3 cases of coarctation of the aorta all pregnant for the first time, the average age being 25. These cases have been previously reported in detail by Mendelson¹⁵ together with a survey of the literature and analysis of the previously reported cases. All had cardiac enlargement and mild cyanosis with slight increase in hue as pregnancy progressed but never intense or accompanied by polycythemia. None had tachycardia during pregnancy but all experienced dyspnea beginning about the fourth month of pregnancy, increasing with the progress of gestation except for slight but definite relief prior to labor at term. The first patient was delivered by elective Cesarean section at term, the dyspnea disappeared within the first 24 hours postpartum, and the subsequent course was satisfactory. The second patient delivered spontaneously after a 4-hour labor during which the pulse and respirations remained at physiologic levels but postpartum the dyspnea became more severe and the general condition markedly worse. Definite cardiac and vascular changes were indicated by the development of a diastolic murmur to the left of the sternum. Cesarean section and tubal sterilization were performed in the third patient shortly after the onset of labor at which time the pulse rate had risen to 120 per minute and the respiratory rate to 30 per minute. Digitalis had been administered prior to operation and was continued for the first 2 days postpartum. The pulse and respiratory rates returned to normal within the first 48 hours and the subsequent course was satisfactory.

Mendelson found 29 other reported cases of coarctation of the aorta complicating pregnancy. The average age was 34 and the average parity 3. There were 5 deaths attributable to the lesion—2 from rupture of the aorta, 1 from cerebral accident, 1 from cardiac failure, and 1 from endocarditis, and in over one-half the cases pregnancy and labor had a deleterious effect upon the patient's condition. With these patients a satisfactory clinical condition does not necessarily indicate a good immediate prognosis for there are the ever-present dangers of aortic rupture, cerebral accident, or valvular damage, and these risks are enhanced by the physiologic mechanisms of pregnancy and labor.

In the present series there were 2 cases of patent ductus arteriosus, the average age being 24 and the average parity 0.5. There was no instance of dyspnea, cyanosis, polycythemia, or any cardiac difficulty during pregnancy, labor, or the puerperium.

Including the series of Couderc and Jensen there are 31 other reported cases of patent ductus arteriosus complicating pregnancy. Jensen found the average age to be 27.2 and the average parity 2.2. There are 6 recorded deaths only 2 of which can be attributed to the lesion—1 died of congestive failure at 5 months' gestation (Schulcz²³) and the other died of congestive failure following Cesarean section

at term (Tunis²⁶). There is no mention of any cardiac difficulty during pregnancy, labor, or the puerperium, in the other cases.

In the present series there was 1 case of patent foramen ovale—a 35-year-old para III gravida V who was free of dyspnea, cyanosis, polycythemia, or difficulty during pregnancy, labor, or the puerperium.

Including the series of Couderc and Jensen there are 18 other reported cases of patent foramen ovale complicating pregnancy. Jensen found the average age to be 32.5 and the average parity 6.6. There are 10 recorded deaths only 6 of which can be attributed to the lesion (Campbell,⁴ Jönen,¹² Porak,¹⁹ Rudaux,²² Perreymond,¹⁸ and Rosemund²¹—the last 2 cases being complicated by other medical conditions). Therapeutic abortion was performed in 1 case which survived (Löwi¹⁴). In the remaining 7 cases there is no mention of any cardiac difficulty during pregnancy, labor or the puerperium.

In the present series there were 2 cases without a specific diagnosis of the congenital anomaly. In neither was there dyspnea, cyanosis, polycythemia or other cardiac difficulty. The one had a normal delivery and the other a spontaneous abortion at 18 weeks.

Although not encountered in this series, mention is made for the sake of completeness of two other rare congenital defects—dextrocardia and congenital hypoplasia of the aorta. Dextrocardia *per se* does not constitute a problem, although the anomaly is frequently associated with other defects. Jensen found 5 cases of isolated dextrocardia in which pregnancy was entirely uneventful. Congenital hypoplasia of the aorta is usually associated with sexual immaturity and is rarely seen in childbearing women. There are in the literature 2 deaths during pregnancy attributed to this lesion, both due to cardiac failure—1 at term (Weibel²³), and the other postpartum (Wagner²⁷), but no other complications are recorded.

The cardiac Functional Capacity of the patients in the present series according to the scheme of the New York Heart Association is seen in Table 2.

Patients with cardiac disease are placed in Class 1 when there is no limitation of their physical activity because of the heart; Class 2 patients show slight limitation of their physical activity by symptoms due to the heart; Class 3 patients show marked limitation by such symptoms on attempting physical activity, while Class 4 patients have such symptoms while at rest and any physical activity will increase these symptoms.

TABLE 2.—RELATION OF PARITY AND CARDIAC FUNCTIONAL CAPACITY.

	Class 1.	Class 2.	Class 3.	Class 4.
Total number of patients	7	9	3	1
Primigravidae	4	4	3	0
Multigravidae	3	5	0	1

It will be noted that 80% of the patients were in Classes 1 or 2. Except for the 1 case of cardiac failure (Case 8) there was no change in the functional capacity during pregnancy, labor, or the puerperium. Classes 2 and 3 patients were admitted for rest, observation, and evaluation at least 2 weeks before term. An increase in parity did not seem to be associated with a more serious cardiac situation, the one case subjected to therapeutic abortion because of heart disease being a primigravida with pulmonic stenosis and marked cardiac enlargement and this patient was successfully delivered at term in a subsequent pregnancy.

It has been customary to administer digitalis to patients in Classes 2 and 3 if the pulse or respirations exceed physiologic levels early in labor prior to the onset of bearing down efforts, as it is believed that impending cardiac failure may be averted or more rapidly and efficiently treated by such procedure. In such patients also the second stage of labor would be eliminated or appropriately shortened by forceps delivery. In the present series digitalization was required in only 2 patients. In 1 of these Cesarean section was performed because of coarctation of the aorta, and in the other there was a complicating lobar pneumonia.

No signs or symptoms of veno-arterial shunt occurred in the group with lesions allowing for such an occurrence although there was no instance of major operative procedure, prolonged second stage, or excessive blood loss among those patients. Prolonged second stage is considered dangerous in this respect because of the possibility of unduly increased pressure in the pulmonary circuit from prolonged and excessive bearing down efforts. The judicious use of outlet forceps should help to reduce the chances of shunt due to these pressure changes. Careful observation during the first 24 hours postpartum failed to reveal any untoward symptoms or physical signs suggesting cardiac embarrassment.

There was no instance of intrapartum or puerperal infection. Congenital cardiovascular defects from a locus minoris resistentiae and with this in mind strict attention is paid to aseptic technique, so that all procedures which increase the likelihood of infection are avoided if possible. Vaginal examinations are omitted, rectal examinations reduced to a minimum, and local anesthesia employed at delivery to guard against third stage hemorrhage. The average third stage blood loss for the series was 167 cc. whereas that for the average clinic patients is 247 cc.

Summary and Conclusions. The majority of patients with serious congenital heart disease succumb before reaching puberty. Those that survive require evaluation if childbearing is contemplated. In addition to the general physical condition, such factors as cardiac functional capacity, the size of the heart, the degree of cyanosis and polycythemia, and the particular lesion merit special consideration. Cyanosis *per se* is not a contraindication to pregnancy.

Pregnancy and labor present such definite risks to patients with coarctation of the aorta that contraception should be practised in this condition. If discovered early in pregnancy therapeutic abortion is indicated, but if gestation is far advanced and interruption from below not feasible, delivery should be effected by Cesarean section and tubal sterilization performed.

Cases of widely patent foramen ovale, interventricular septal defect, and patent ductus arteriosus form another special category by virtue of the possibility of veno-arterial shunt. Such an occurrence has not been observed in this series but certain precautions should be taken to avoid the possibility of the rare but serious accidents referred to in the literature. Arterial blood pressure should be maintained by avoiding traumatic procedures and postpartum hemorrhage, or by promptly instituting appropriate therapeutic measures in the event of such occurrences. Local anesthesia at delivery will decrease third stage blood loss and the judicious use of outlet forceps will obviate undue bearing down efforts with resulting increased pressure in the pulmonary circuit. Particular attention should be paid to the avoidance of infection.

Classes 2 and 3 patients should be admitted several weeks prior to term for rest and study. In such patients with cardiac enlargement digitalis should be used if the pulse or respiratory rate exceeds physiologic levels early in labor, before the onset of bearing down efforts. The second stage of labor should be eliminated for these patients or appropriately shortened by forceps delivery. Careful observation should extend throughout the first 24 hours postpartum.

The difference between the lack of mortality in this series and the 11% mortality reported in the 135 cases from the literature is surprising. We encountered only 1 patient in Functional Class 4 and 3 patients in Class 3. If 2 or 3 of these had died there would have been a mortality in our series comparable to the figures in the literature. We realize that there is a tendency for the literature to contain the most severe cases and particularly cases that have died, because these are likely to afford a more exact diagnosis through the possibility of an autopsy being performed. We would like to think that our low mortality is in part at least due to the care with which our patients have been followed and particularly to the attempts which were made by using rest and digitalis and appropriate obstetrical procedures to save those patients with any signs of cardiac insufficiency from encountering a strain during pregnancy or labor which might have been harmful.

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PREGNANCY AND THE DEVELOPMENT OF MAMMARY CANCER.*

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THE 2 clinical cases that we report below and the facts that became apparent in the course of this study suggest a certain number of reflections. We shall begin by describing the evolution of the process in the 2 cases and then present the connections that we feel justified in making.

Case Reports. CASE 1.—Madam S, aged 35, had been treated up to 1937 for a calculous cholecystitis with several crises of hepatic colic. In 1937, following a double postpartum phlebitis, which required 2 months in bed, this patient noticed several lumps in the upper part of her right breast. She consulted a number of physicians and surgeons all of whom agreed in the diagnosis of benign adenomata. This was confirmed by histologic examination of a nodule removed at biopsy. Up to 1939 the patient remained in excellent health, continuing her daily work. The breast nodules, examined on several occasions, showed nothing suspicious. There was no adenopathy or evidence of malignant change, but rather a progressive diminution in size.

The patient went through a normal pregnancy beginning in June, 1938. She was delivered of a normal infant at term, and had a normal lactation period. But 10 days after her delivery, before leaving the hospital, there was noticed in the upper part of the greatly enlarged lactating breast, at the level of the biopsy scar, an induration about half the size of a hen's egg. This induration had not been present on the day of her delivery. This

* Difficulties of transatlantic correspondence have prevented the author from correcting the proof of this article. It has also been impossible to secure from him illustrations or a completed list of references.

mass, opaque to transillumination, made us fear a carcinoma of the breast. There was already in the axilla a small but hard and mobile lymph node. This, with the reservations necessary for the frequency of errors in clinical diagnosis in this field, appeared to have neoplastic characteristics in spite of the rapidity of its appearance.

There was nothing abnormal in the supraclavicular region; radiologic examination of the thorax showed no change that could be interpreted as neoplastic. The laboratory reported nothing abnormal except a marked increase of the blood cholesterol.

Our advice to the family was as follows: in view of the patient's postpartum asthenia, to commence radiotherapy of the neoplastic region and of its proximal vascular zone, to be followed later by a surgical excision of the mammary and maxillary region. To our great regret, the patient refused radiotherapy because her mother-in-law had died following Roentgen ray therapy. We therefore with the patient's approval decided on surgical operation. This was carried out without incident, according to Halsted's method, and the material referred to M. Peyron, of the Pasteur Institute, for pathologic study. *Microscopically*, the large mammary gland was covered at the level of the neoplasm by a thickened skin that looked like the skin of an orange. The gland was heavy and in a number of areas round nodules were palpable that suggested adenoma. On section, an epithelial tumor was found, hard, not circumscribed, and presenting a white gelatinous appearance. Histologic examination of a number of sections from different parts of the mass revealed a glandular carcinoma with large cells occurring in a loose connective tissue framework. The neoplastic cells were markedly pleomorphic, mostly large and either rounded or elongated with irregular outlines. The protoplasm was clear with an irregular, often fragmented nucleus and other signs of degeneration. The frequent mitoses were atypical, sometimes multipolar. The acini were atrophic, the ducts dilated and contained more or less necrotic debris. The lymph nodes were congested with capillary dilatation. There was marked histiocytic reaction in the connective tissue. No neoplastic cells were found anywhere. The nodules scattered through the mammary gland proved microscopically to be cystadenomata without malignant degeneration.

CASE 2.—A woman, aged 40, had no relevant family history; had had lobar pneumonia at 25 years of age, a mammary abscess after her first pregnancy at 28 years, and suffered since youth from a chronic gastritis.

At the age of 10 she had had an adenoma of the breast removed. Numerous microscopic examinations confirmed the benign adenomatous nature of this tumor. In addition, her general condition and the clinical aspect of the tumor gave no doubt as to its benignancy.

At 35 the patient again became pregnant without postpartum complications or aggravation of the tissues formerly operated upon. In January, 1939, at the age of 40 and when 8½ months pregnant, the patient noticed in the mammary scar a nodule which had not been there before. This did not have the typical clinical appearance of an epithelioma of the breast, but 10 days before delivery it rapidly increased in size. This induration became about the size of a hen's egg and showed the clinical signs of an epithelioma. There was also a hard and slightly movable adenopathy in the axilla. The operation took place under good circumstances. The tissue, studied grossly and microscopically, showed epithelial masses. The cells were very pleomorphic, mostly cuboid and cylindrical. There was a complete change in the architecture of the organ. Gigantic and mitotic cells were particularly numerous, showing the malignant nature of the tumor and explaining the invasion of the adjacent tissue and the malignant involvement of the axillary lymph nodes.

Comment. These clinical and pathologic data in our 2 patients made it desirable to consider the biologic problem of the relation between pregnancy and the development of cancer. We shall not discuss all the opinions that have been given on this subject, but wish to emphasize in these 2 cases the brusque appearance during the preparatory stage of lactation, of epitheliomas in the old scars of adenomas; in other words, when physiologic factors were determining changes in the mammary tissue of a pregnant woman.

It is difficult to obtain a precise idea about the development of mammary cancer during pregnancy or after delivery. Certain authors maintain that pregnancy and the puerperium favor the development of mammary cancer, incriminating the follicular hyperplasia incident thereto. Others, however, preach the contrary. The statistics of human pathology, and clinical and laboratory research in experimental cancer of animals, have not only not given conclusive results, but have even been contradictory. In human pathology, Lacassagne, who was able to produce a mammary cancer in male mice by injections of folliculin, has shown that folliculin arrives in abundance in the human mammary gland while this organ is being congested with blood. The colostrum contains folliculin in considerable amount, at least equal to that found in the urine. It is therefore probable that the mammary congestion in the menstrual period is also accompanied by the passage of hormones into the mammary cells and mammary ducts where it may accumulate. All this tends to establish that some women may retain folliculin either in the mammary glands as a whole or in parts of them. As a result of the prolonged irritation of the epithelium of the ducts a hypersecretion is produced, then epithelial overgrowth, and finally a proliferation with infiltrating tendencies—carcinoma. Furthermore, Micale has shown that the puerperium favors the development of cancer and incriminates the hyperfolliculinism of pregnancy. The American authors, Goormaghtigh, Armerlink, and others who have published lengthy studies on this subject, arrive at the same conclusion, namely that in human pathology the hyperfolliculinism of pregnancy and the puerperium are carcinogenic factors.

Among those who preach the contrary views, let us cite Bentioglio, who observed a case of leukemia that was improved after childbirth. Simonnet also does not believe in the production of cancer of the breast by hyperfolliculinism. This author however admits that folliculin can favor cellular development, but without tendency toward cancer. Thus in human pathology this problem has not given consistent results.

Let us pass now to the domain of experimental cancer. The principal authors who have studied the carcinogenic effect of pregnancy and puerperium in laboratory animals are Lacassagne,

Amandio Tavares, Loeb, Murray and Simonnet. Lacassagne has produced a mammary cancer in the male mouse by the injection of folliculin, and has studied the causes of the development of cancer in folliculinized mice as well as the varied action of folliculin in various strains of mice. It appears indisputable, he says, that the adenocarcinoma of mice is the result of a prolonged stimulus to proliferation that is exercised by folliculin on the cell of the mammary gland.

In the same way Amandio Tavares and Ernesto Morais have studied the influence of ovarian castration on the development of tar tumor in rabbits. In the first group both ears of 25 bilaterally castrated rabbits were painted from the 7th or 8th days after castration. The applications were made twice a week for 7 months. A second group of 25 rabbits were painted only, to serve as controls. In the 25 castrated rabbits 10 died from the 5th to 77th day after the application was begun without developing tumors. The first papilloma appeared on the 34th day, most of them developing before the 80th day. In this group 3 carcinomas developed, controlled histologically on the 62d, 151st, and 206th day. In the controls 11 died without any neoplastic development between the 3d and 125th day. The first nodule appeared on the 18th day, and 5 cases of carcinoma were diagnosed by biopsy (21st, 64th, 69th, 155th and 158th days). Comparing the results of these two series, the authors note that the castrated rabbits withstood the tarring as well as the normals and that most of the nodules had accomplished their development in both groups before the 80th day.

Concerning the evolution of the tumors, there were noted in a period of 7 months histologically malignant neoplasms in 3 castrated females as opposed to 5 in the control rabbits. The development of cancer was not only a little more frequent but more precocious in the latter group, to which belonged the one example in these experiments of a precocious cancer (*i. e.*, diagnosed histologically before the 30th day). One may infer, then, that castration rendered the terrain less propitious to the development of tar cancer. These facts tend to confirm the inhibiting effect of castration and to suggest the influence of sexual hormones on the tumor development. The authors remark, however, that in these as in former experiments their observations show the importance of individual susceptibility in the pathogenesis of experimental cancer. The tumor nodules were not regularly either more numerous or larger in the normal rabbits than in those deprived of their sex glands. In both groups there were observed examples of rapid or slow growth, persistent or transient duration. Also, they obtained two excellent examples of ulcerating carcinoma in the castrated rabbits. Loeb and Murray have produced adenocarcinoma of the breast in mice by the repeated injections of large doses of folliculin ben-

zoate. With smaller doses only doubtful results were obtained. These tumors were produced in strains of mice in which the males did not produce spontaneous cancer. The frequency of the lesions appears to be a function of the greater or lesser sensibility of the strains of mice to folliculin (Lacassagne). After a certain age the heredity factor appears not to play any part. Lacassagne, Goormaghtigh and Amerlink have given a detailed description of these lesions.

The cutaneous application of folliculin can also provoke a mammary carcinoma in the male mouse (Burrows). Schockaert also attributes the stimulating effect of pregnancy and delivery on the development of mammary cancer to the hyperfolliculinemia of pregnancy and the puerperium. The structural and functional changes that occur in the mammary gland during the sexual cycle have an interesting repercussion on the problem of mammary cancer.

It is especially Simonnet who combats these views concerning the experimental production of cancer by folliculin. In his thesis entitled "The Role of the Follicular Hormone in Normal and Pathological Physiology," he writes "How shall we interpret the role of folliculin in the development of tumors?" Folliculin, he says, can stimulate cell development, but has no influence on the speed of mitoses. It provokes them but does not hasten them. It can also in exaggerating a physiologic process favor the action of a carcinogenic agent, but it does not appear to be a carcinogenic agent itself. Other observations made by Babes and Buclear on this subject, which offer from a biologic point of view some advantages that will not be insisted upon here, have not produced concordant results. While Babes alludes to an ovarian hyperplasia in the tarred rabbits caused by a multiplication of interstitial cells, Buclear opposes this interpretation and regards the ovarian hyperplasia as connected with the estrus period during which the ovaries were removed.

American investigators who are in accord on the carcinogenic effect of folliculin have proposed castration or ovarian blockade by Roentgen ray of women who have carcinoma of the breast in order to prevent recurrences and metastases. Adair and Pack, who with many pathologists accept the rôle of milk stagnation in the production of mammary cancer in the family, have proposed the aspiration of the stagnant milk with an electric pump. Instead of this mechanical treatment, may one not look hopefully for a hormone antagonistic to folliculin, perhaps a galactogenic hormone which would permit an evacuation at will of the products cyclically accumulated in the mammary glands? We may mention also that the laboratory shows that hyperfolliculinism is almost constant in tumor patients: the blood of those who have malignant tumors

contains up to 9000 mouse units per liter, the urine up to 5000 mouse units per liter.

In the presence of such inconclusive and even controversial results, we may well ask what then was the factor other than folliculin, which made the malignant tumor appear in our 2 patients after delivery?

Summary. Our two observations concerned the clinical history of 2 multiparae each of whom previously had had an adenoma of the breast removed and developed a carcinoma in the scar during a subsequent pregnancy. It is obvious that in these 2 cases there was a close connection between the preparation for lactation and the development of cancer in the previously adenomatous breast. Without discussing the pros and cons of the question of the influence of pregnancy and the puerperium on the genesis of cancer, we wish to emphasize the sudden appearance of a carcinoma in an old scar of an adenoma at a time when a physiologic manifestation of the mammary tissue was in progress. We are in accord with those cancer investigators who think that the hyperfolliculinism of pregnancy favors the development of mammary cancer. Should one attribute this to the prolonged irritation of the mammary epithelium by folliculin, or perhaps to the loss of equilibrium (neurovegetative, vascular, hormonal) that accompanies the change from the stable condition of the 9 months of pregnancy to the puerperal state, a change which is capable of provoking pathologic activity of a carcinogenic nature?

We believe also that the amount of folliculin plays its rôle in the genesis of cancer. We know that Roentgen rays in sufficient doses may kill the cancer cell, but in smaller doses may provoke cancer (the cancer of the radiologists). Colchicine stimulates or inhibits mitosis according to the dosage. The same variation might occur with folliculin. No doubt the therapeutic abuse of folliculin might in some cases favor the development of cancer. We may also hope for a hormonal antagonist to folliculin which would permit the evacuation or the destruction of harmful substances periodically emptied into the blood.

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CONCENTRATED LIVER EXTRACT IN THE MAINTENANCE TREATMENT OF PERNICIOUS ANEMIA.

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DURING the last 2 or 3 years an effort has been made by a committee appointed for revision of the United States Pharmacopœia to rate the efficacy of various manufactured substitutes for whole liver. A great deal has appeared in the literature concerning the use of unconcentrated liver extract in large doses and there seems to be no question that the various preparations given in 10-cc. doses are effective. A number of reports from foreign countries have been studied in this respect. Most of these are concerned with the use of extract given in 5-cc. doses. Writers from foreign areas apparently consider this a concentrated form of extract. The preparation most widely used by these workers is "Campolon."* Thus Bell,¹ Hoff,¹⁴ Meulengracht,^{18a,b} Schittcnhelm,²² Schultcr,²³ Wendt,²⁴ and others^{11,13} have reported on the results obtained from doses of 5 cc. or more. In 1938 Murphy and Howard²⁰ reviewed 31 cases which they had treated with 1-cc. doses of Lederle's Concentrated Liver Extract. Their tables on their own results and on those of others are available for study. With the exception of Murphy and Howard's²⁰ and Hartfall's¹² series, no reports of cases treated with doses of less than 3 cc. are quoted by them.

This contribution deals mainly with maintenance of the patient with pernicious anemia in a state of well-being and good health particularly under treatment with "Reticulogen."† The clinical material used in the analysis is derived mainly from the hematology clinic of the New Haven Dispensary where we have treated 31 cases of proven pernicious anemia with Reticulogen. In addition, we have incorporated the results of 9 private cases. No attempt to select favorable cases has been made. All new cases coming to the dispensary during the past 3 years have been subjected to Reticulogen therapy unless there was some special reason for use of another preparation. In addition, a certain number of cases which had been treated by other means were transferred to Reticulogen. Some persons have been kept on other forms of therapy to serve as controls. As controls we have also individuals

* A Liver Extract, product of Winthrop and Company.

† Extremely Concentrated Liver Extract, product of Lilly and Company.

who were formerly on oral liver or less concentrated extracts* and who are now maintained on Reticulogen.

A considerable portion of the liver extract used in this study was contributed by the makers (Eli Lilly & Co.) and the patient was thereby relieved of approximately one-half of the expense of treatment over a 2-year trial period. In the tables "cost" is computed to include this item at ordinary hospital prices so that it refers to the amount which the patient would have had to pay under ordinary circumstances. What this group of patients actually paid is approximately one-half of this amount.

TABLE 1.—RESULTS OF 12 CASES TREATED WITH ORAL LIVER EXTRACTS.

Case,† Name.	Age, Sex.	Treatment (wks.).	Interval (wks.).	Preparation liver ext.	Aver. R.B.C. (millions per c.mm.).	Aver. Hb., %.	Cost per week.
1. M. B.	58 F	208	Daily	Lextron	2 7	75	\$3
2. E. B.	53 M	180	Daily	Squibb's	5 0	97	\$2
3. I. B.	60 F	104	Daily	Lilly's	4.5	99	\$3
4.							
5.							
6.							
7. B. F.	48 F	72	Daily	Squibb's	3.6	78	\$3
8.							
9.							
10. H. H.	55 F	156	Daily	Squibb's	3 9	80	\$1
11. R. H.	48 F	130	Daily	Squibb's	3.6	81	\$4
12.							
13.							
14. D. McK.	43 F	300	Daily	Raw liver	4 5	87	?
15.							
16.							
17.							
18.							
19.							
20. F. N.	65 F	104	Daily	Squibb's	4 0	87	\$1
21.							
22.							
23. G. P.	49 F	170	Daily	Squibb's	3 9	80	\$1
24. H. P.	67 F	60	Daily	Squibb's	3 7	80	\$1
25.							
26.							
27. L. M. S.	65 F	130	Daily	Squibb's	4 0	81	\$1
28. M. S.	46 F	130	Daily	Squibb's	3 5	78	\$1

Patients who had either chronic complicating disease or acute episodes were not excluded from this report and, in some instances, this fact accounts for results which are not completely satisfactory.

Two patients have been treated for only 2 years; the rest have all been treated for 3 or more years.

Results. The standards which we have applied as the measure of the success of treatment include: Red Blood Cell Counts; Hemoglobin Percentage; Improvement in Patients' General Symptoms; Return to or Continuance in Occupation; Neurologic Symptoms and

* Some of the less concentrated liver extracts are: Abbott's Liver Extract, Campolon, Lilly's Concentrated Liver Extract.

† Case numbers, which are not continuous here, refer to the cases in Table 3.

Signs; Ability to Combat Chronic Associated Disease; and Ability to Withstand Acute Intercurrent Infections.

Red Blood Cell Counts and Hemoglobin Percentage. Our results are not as spectacular in the maintenance of these levels as are those of Murphy and Howard, but they do compare favorably with the reports of others,^{2,4,6,9a,b,10,11,15,16} with patients under the care of Reznikoff,²⁵ at New York Hospital and with counts of the man or woman in average health in New Haven. In this regard it must be remembered that we have not selected our cases and that our patients are drawn for the most part from the poorer strata of society.

TABLE 2.—RESULTS OF 12 CASES TREATED WITH LILLY'S CONCENTRATED LIVER EXTRACT.

Case.* Name.	Age. Sex.	Treat- ment (wks.).	Inter- val (wks.).	Units per dose.	Aver. R.B.C. (millions per c.mm.).	Aver. Hb., %.	Neurol. findings.	Cost per week.
1.								
2. E. B.	61 M	75	2	20	4 5	90	Sub. imp.	\$ 25
3. I. B.	61 F	52	2	20	4 8	94	.	\$ 25
4.								
5. D. F.	41 F	30	2	20	4 0	88	Sub. imp.	\$ 25
6. K. E.	68 F	104	2	20	4 0	88		\$ 25
7. B. F.	49 F	68	2	20	4 0	88		\$ 25
8. P. G.	58 M	100	2	20	4 8	96	Sub. imp.	\$ 25
9.								
10.								
11. R. H.	46 F	130	2	20	4 7	94	..	\$ 25
12. B. K.	40 F	150	2	20	4 6	88	...	\$ 25
13.								
14.								
15.								
16.								
17.								
18.								
19.								
20. F. N.	62 F	180	2	20	4.6	85	..	\$ 25
21.								
22.								
23. G. P.	50 F	104	2	20	4 3	86	Sub. imp.	\$ 25
24.								
25.								
26.								
27.								
28. M. S.	47 F	104	2	20	4 2	84		\$ 25
29. M. Wa.	70 F	64	2	20	4 5	97		\$ 25
30.								

* Case numbers, which are not continuous here, refer to the cases in Table 3.

General Symptoms. Nearly all the patients have noted either maintenance of previous good health or actual improvement in sense of well-being. Most of our patients have either continued to work at gainful occupations or have been restored to usefulness. Six were not able to work at the onset of therapy and are still unable to do very much. Eight were unable to work when Reticulogen was

started but are now returned to full function. Nearly every patient has gained weight and strength.

Neurologic Symptoms and Signs. Under subjective improvement we include such symptoms as relief from numbness and tingling, improved sense of well being, increased capacity for work and increased certainty in walking.

During the years when oral whole liver or liver extract were used, notes on the neurologic findings were few and so we have not tabulated them in this study. When the period of parenteral therapy was reached notations as to neurologic state became more frequent but were not made in many cases. Of the 12 cases treated by 5-cc. doses of Lilly's Concentrated liver extract 4 were noted to have had improvement in symptoms. The other 8 patients were at least maintained in *statu quo* and may have actually improved subjectively although the notes are not full enough to say positively. During the years of treatment with Reticulogen particular attention was paid to subjective and objective improvement in the neurologic state. Thirty-two of the cases have given evidence of symptomatic improvement; 8 have shown no improvement, but of these 4 (Cases 6, 15, 23 and 30) complained of no neurologic symptoms at the onset of treatment and are therefore considered to have been protected from their development during treatment. Four cases have shown no improvement or have actually become worse. Case 19 was very irregular in attendance at the clinic. Case 31 was complicated by epilepsy with frequent and severe convulsions. Case 24 was a very frail woman with chronic (quiescent) tuberculosis who passed through an attack of Type III pneumonia before the treatment with sulfathiazole was known and recovered to her previous health level and who later weathered one gall bladder operation but succumbed to a second one for adhesions.

Evidence of objective improvement has been found in numerous instances and has been substantiated by the kind coöperation of the neurologic division of the dispensary.

Gait. Twenty-one patients have shown improvement in gait which has been very marked in certain instances. Thus Cases 18 and 38 were completely bedridden at the onset of treatment and were restored to complete function and maintained with full ability to walk.

Vibratory Sense. Eleven of our patients have retained the normal response to vibratory stimuli; 21 have actually regained some portion of it, where it was absent when therapy was commenced.

Reflexes. Thirteen patients with relatively normal reflexes have been maintained in that state during treatment; in 17, improvement has been noted in this particular respect in those cases where reflexes were absent at onset of therapy.

Sphincter Control. During Reticulogen therapy 3 of our patients have regained a considerable amount of urinary sphincter control.

Mental Symptoms. In many instances memory has improved remarkably. Most of the persons under treatment have shown release from an unfriendly and suspicious attitude toward physicians and nurses. Patients who were uncoöperative at the start have become very helpful and trusting. Practically all who have had treatment for 6 months or more have no desire to stop because they appreciate so well the value they have received from it.

Complication by Chronic Disease. Sixteen patients have arteriosclerosis sufficiently advanced to be evident clinically. Four have arteriosclerotic heart disease. One has lived through two cerebral hemorrhages. Three have chronic gall bladder disease and have survived several acute attacks. One has developed signs of cirrhosis of the liver and has suffered a fracture of the surgical neck of the femur. Two have myxedema and 2 have thyrotoxicosis (1 of these had a thyroidectomy during the course of our therapy). Two have quiescent tuberculosis and 1 has developed acute exacerbations of tuberculosis without disturbing very much the blood picture. One has frequent and severe seizures of epilepsy and is being treated with dilantin. Three have syphilis—are under the usual forms of therapy, and 3 have chronic infectious arthritis.

Complications by Acute Disease. Nearly all have had mild upper respiratory disease on 1 or more occasions. Fifteen have had severe respiratory disease usually diagnosed as "grippe" or "influenza." Three have survived pneumonia. One has been successfully carried through 2 pregnancies. One had no major change in her blood status when thyroidectomy was performed.

It has seemed to us that these individuals, in spite of their pernicious anemia, have carried on about as well under these vicissitudes as does the average man under the same circumstances.

FOOTNOTE FOR TABLE 3.

Of these 40 cases, 12 had previously been treated for long periods with oral liver preparations (Table 1), and 12 with Lilly's Liver Extract (Table 2).

"Interval (weeks)" = number of weeks between treatments.

"Aver. R.B.C." and "Aver. Hg." = average level of maintenance of these factors.

"Hemat." = hematocrit reading; "M.C.V." = mean corpuscular volume; "M.C.H." = mean corpuscular hemoglobin; "M.C.H.C." = mean corpuscular hemoglobin %. These factors were determined at various times during the course of the disease, the high levels of M.C.V. being in those instances where the tests were done at or near the beginning of treatment (Cases 1, 8, 28). The rest were completed after maintenance was considered to have been attained.

"Sub. imp." = subjective improvement.

"Gait, First and Last" refers to state at first and last examination of patient. "Imp." stands for improvement.

"Vibratory sense" and "Reflexes" also contain two lists under the headings of "First and Last." In these columns "Abs." refers to absence of the reflexes or vibratory sense; "Dim." to diminished and "Imp." to improved.

"Nor." refers to cases where the signs were not present at onset and did not develop during treatment.

The same terms and meanings are used in other tables.

* Private cases.

TABLE 3.—RESULTS OF 40 CASES TREATED WITH RETICULOGEN.

Case.	Name.	Age.	Sex.	Treatment (weeks.)	Interval (weeks.)	Units per dose.	Aver. R.B.C. (mills. per c.mm.).	Aver. hg. (%).	Hemat.	M.C.V.	M.C.H.	M.C.H.C.	Neurologic findings during treatment with reticulogen.						Complications.	End-results.				
													Sub. imp.	Gait.		Vibratory sense.		Reflexes.			Mental.	Cost per week (dollars).		
														First.	Last.	First.	Last.	First.					Last.	
1.	M.B.	62	F	130	3	20	4.7	88	..	135	44	32	Yes	Poor	Imp.	Abs.	Imp.	Dim.	Imp.	Nor.	.25	Art. scler.	Health maintained; working.	
2.	E.B.*	61	M	208	4	20	5.0	90	Yes	Abs.	Abs.	Abs.	..	Nor.	.20	Art. scler.; cor. hem.	Blood status good; not working.	
3.	L.B.	62	F	118	3	20	4.8	94	47	90	28	31	Yes	Poor	Imp.	Abs.	Imp.	Dim.	Imp.	Imp.	.30	Art. scler.	Health good; working.	
4.	G.C.	62	F	117	4	20	4.9	94	46	92	31	34	Yes	Poor	Imp.	Dim.	Imp.	Dim.	..	Nor.	.20	None	Health good; working.	
5.	R.d.P.	42	F	102	3	20	4.5	88	42	97	33	33	Yes	Nor.	Nor.	Nor.	Nor.	.30	None	Health good; working.	
6.	K.E.	72	F	97	2	20	4.2	84	42	97	34	35	Nor.	Nor.	Nor.	Nor.	Nor.	.25	Art. scler.; grippe	Health good; working.	
7.	B.F.	50	F	107	3	20	4.3	88	42	102	33	32	Yes	Poor	Imp.	Abs.	Imp.	Dim.	Dim.	Nor.	.25	None; chr. bronchopneum.	Health good; working.	
8.	P.G.	62	M	128	3	20	4.8	88	45	107	33	32	Yes	Poor	Imp.	Abs.	Imp.	Dim.	Dim.	Same	.20	Chr. inf. arthritis; bronchopneum.	Not known; working when last known.	
9.	C.H.	53	M	90	4	20	4.4	88	Yes	Nor	Nor.	Dim.	Imp.	Dim.	Imp.	Nor.	.10	Psychiatric breakdown	Health good; working.	
10.	H.I.	58	F	152	2	10	4.5	88	39	98	34	35	Yes	Poor	Imp.	Dim.	Imp.	Dim.	Imp.	Nor.	.40	Cat. jaundice; chr. gall bl.	Blood status good; not working.	
11.	R.I.	51	F	122	4	10	4.0	90	45	107	34	32	Yes	Poor	Imp.	Dim.	Imp.	Dim.	Imp.	Nor.	.30	Thyrototoxicosis; card. dis.	Blood status good; working.	
12.	B.K.	43	F	132	2	20	4.5	86	42	100	33	33	Yes	Poor	Imp.	Dim.	Imp.	Dim.	Imp.	Nor.	.15	Art. scler.; grippe	Health good; working.	
13.	F.K.	69	F	152	3	20	4.8	94	43	95	31	32	Yes	Poor	Imp.	Abs.	Imp.	Dim.	Imp.	Nor.	.30	Sensitive to Lederle's	Health good; working.	
14.	D.McK.	49	F	110	4	20	4.4	88	Yes	Nor.	Nor.	Abs.	Imp.	Dim.	Imp.	Nor.	.20	Art. scler.; grippe	Health good; working.	
15.	F.MeL.	35	M	80	3	10	4.8	97	45	95	30	31	Yes	Poor	Imp.	Dim.	Imp.	Dim.	Imp.	Nor.	.15	None	Art. scler.; bronchopneum.	Blood status good; not working
16.	R.MeQ.	69	F	118	3	20	4.7	94	45	95	30	31	Yes	Poor	Imp.	Dim.	Imp.	Dim.	Imp.	Nor.	.20	Diabetes; thyrotoxi.; thyroidec.	Health good; working.	
17.	M.M.	74	F	123	4	20	4.3	86	43	100	30	30	Yes	Poor	Imp.	Abs.	Imp.	Abs.	Imp.	Nor.	.40	Art. scler.; grippe	Health good; working.	
18.	M.Mi.*	51	F	144	3	10	5.0	95	45	95	30	30	Yes	Lost	Imp.	Abs.	Imp.	Abs.	Imp.	Nor.	.15	None	Art. scler.; bronchopneum.	Blood status good; not working
19.	T.M.	60	F	138	4	10	4.0	81	22	100	32	32	No	Poor	Imp.	Abs.	Imp.	Nor.	Nor.	Nor.	.20	Art. scler.	Health good; working.	
20.	F.N.	67	F	116	4	20	4.7	88	Yes	Poor	Imp.	Abs.	Abs.	Dim.	Dim.	Nor.	.40	Art. scler.	Health good; working.	
21.	M.F.*	76	F	156	2	20	4.5	90	Yes	Poor	Imp.	Dim.	Dim.	Dim.	Dim.	Nor.	.40	Chr. inf. arthritis; bronchopneum.	Health good; working.	
22.	M.O.C.	43	F	97	2	20	4.6	91	Nor.	Nor.	Nor.	Abs.	Abs.	Abs.	Abs.	Nor.	.40	Chr. inf. arthritis; Type III pneu.	2 Gall bladder operations. Died.	
23.	G.P.	53	F	137	2	20	4.4	85	43	105	33	31	Nor.	Nor.	Nor.	Abs.	Imp.	Nor.	Nor.	Nor.	.30	None	Health good; working.	
24.	H.P.	63	F	112	3	20	4.3	88	Yes	Poor	Imp.	Abs.	Abs.	Abs.	Abs.	Nor.	.40	Hyp. prostate; prostatic.; art. scler.	Health good; recovering from oper.	
25.	H.R.	55	M	112	3	20	4.0	80	39	93	29	31	Yes	Poor	Imp.	Dim.	Imp.	Abs.	Same	Nor.	.30	Myxedema; cat. jaund.; chr. gall bl.	Blood status good; not working.	
26.	M.R.	66	M	80	3	20	4.7	94	..	96	33	34	Yes	Poor	Imp.	Abs.	Abs.	Abs.	Same	Nor.	.30	Complete loss of hair; myxedema	Health good; working.	
27.	L.M.S.	68	F	100	3-1	20	3.8	73	No	Poor	Imp.	Nor.	Nor.	Nor.	Nor.	Nor.	.40	Chr. inf. arth.; cirr. liver; frac. femur	Blood status good.	
28.	M.S.	50	F	117	3	20	4.5	90	45	105	34	32	Yes	Poor	Imp.	Abs.	Abs.	Abs.	Abs.	Nor.	.40	Epilepsy; dilantin treatment	Blood status good; not working.	
29.	M.Wa.	74	F	131	2	20	4.5	86	Yes	Poor	Imp.	Dim.	Imp.	Abs.	Abs.	Nor.	.40	2 Pregnancies	Health good; working.	
30.	M.Wc.	73	F	121	2	20	4.6	94	43	99	31	32	No	Poor	Imp.	Dim.	Imp.	Abs.	Abs.	Nor.	.20	Art. scler.; sensitivity	Health good; working.	
31.	B.W.	34	F	145	3	20	4.3	88	42	95	33	35	Nor.	Nor.	Nor.	Dim.	Imp.	Dim.	Imp.	Nor.	.30	Art. scler.	Health good; working.	
32.	Bcr.	39	F	129	2	10	4.4	88	39	89	29	33	Yes	Poor	Imp.	Dim.	Imp.	Dim.	Imp.	Nor.	.20	Art. scler.	Health good; working.	
33.	K.Z.	70	F	127	2	10	4.4	88	43	86	30	35	Yes	Poor	Imp.	Dim.	Imp.	Dim.	Imp.	Nor.	.30	None	Health good; working.	
34.	P.F.*	55	M	72	3	20	4.5	90	41	95	31	35	Yes	Poor	Imp.	Dim.	Imp.	Dim.	Imp.	Nor.	.30	Art. scler.	Health good; working.	
35.	L.A.*	62	F	86	3	10	4.4	83	Yes	Poor	Imp.	Dim.	Imp.	Dim.	Imp.	Nor.	.30	None	Health good; working.	
36.	M.J.*	49	F	107	3	20	4.3	85	Yes	Poor	Imp.	Dim.	Imp.	Dim.	Imp.	Nor.	.30	Art. scler.	Health good; working.	
37.	A.L.*	69	M	92	3	10	4.2	84	Yes	Abs.	Imp.	Abs.	Imp.	Abs.	Imp.	Imp.	.30	Art. scler.	Health good; working.	
38.	J.L.*	51	M	102	1	20	4.7	86	Yes	Abs.	Imp.	Abs.	Imp.	Abs.	Imp.	Imp.	.80	None	Health good; working.	
39.	J.S.*	61	F	140	2	10	4.4	84	Yes	Nor.	Nor.	Nor.	Nor.	.20	None	Health good; working.	

TABLE 4.—FURTHER CASES TREATED WITH LILLY'S CONCENTRATED LIVER EXTRACT.

Case.	Name.	Age.	Sex.	Treatment (weeks).	Interval (weeks).	Units per dose.	Aver. R.B.C. (mills. per c.mm.).	Aver. Hg. (%).	Hemat.	M.C.V.	M.C.H.	M.C.H.C.	Gait.		Vibratory sense.		Reflexes.		Mental.	Cost per week (dollars).	Complications.	End-results.
													First.	Last.	First.	Last.	First.	Last.				
1.	E.B.	61	F	211	2	20	4.5	90	47	107	35	33	Yes	Poor	Imp.	Abs.	Dim.	Imp.	Imp.	.25	Art. scler.; grippé	Health good; working.
2.	J.B.	37	M	200	2	20	4.8	91	Yes	Nor.	Nor.	Dim.	Nor.	Nor.	Nor.	.25	Tb.; pncu.	Worked during 3 years' treatment.
3.	H.B.	65	M	204*	2-6	20	4.0	80	No	Poor	Poor	Dim.	Dim.	Dim.	Nor.	.25	Fracture tibia	Worked during 3 years' treatment.
4.	B.B.	56	F	235	2	20	4.8	95	44	88	29	32	Yes	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.	.25	None	Working.
5.	M.C.	53	F	235	2	20	4.5	90	42	91	29	32	Yes	Poor	Imp.	Dim.	Nor.	Nor.	Nor.	.25	None	Working.
6.	H.E.	75	F	150*	2-10	20	3.0	80	31	82	28	34	Yes	Nor.	Nor.	Dim.	Abs.	Abs.	Nor.	.25	Art. scler.; grippé	Working.
7.	W.F.	62	M	150	2	20	4.2	85	45	105	33	31	Yes	Nor.	Nor.	Dim.	Dim.	Dim.	Imp.	.25	Syph.; pncu.	Working.
8.	E.G.	78	M	233*	2-10	20	4.2	88	38	102	34	33	Yes	Nor.	Nor.	Dim.	Dim.	Dim.	Nor.	.25	Art. scler.; cancer of penis—removed	Not working.
9.	F.K.	53	F	180	3	20	4.5	90	44	88	29	33	Yes	Poor	Imp.	Abs.	Abs.	Imp.	Imp.	.25	None	Not working.
10.	A.M.	52	F	204	2	20	4.3	88	42	97	31	32	Yes	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.	.25	Venices removed	Working; was completely disoriented nt onset of treatment.
11.	M.M.	50	F	224	2	20	4.7	96	41	91	31	35	Yes	Nor.	Nor.	Nor.	Nor.	Nor.	Nor.	.25	None	Working.
12.	D.S.	66	M	100	2	20	4.4	90	47	110	30	26	Yes	Nor.	Nor.	Dim.	Dim.	Nor.	Nor.	.25	None	Working.

* Attendance very irregular.

Discussion. If other workers agree with our findings and those of Murphy and Howard,²⁰ that very concentrated forms of liver extract are efficacious, the benefits derived by patient and physician should prove to be considerable. First, the patient is spared a very considerable amount of discomfort, 5-cc. doses being more uncomfortable than the 1-cc. dose. Second, the expense of Reticulogen is not notably larger than that of Lilly's Concentrated Liver Extract and both these preparations compare favorably in price with any of the others.* Third, with the more intelligent patients and particularly those in private practice, a large saving is effected by the fact that some member of the family can be taught to give 1-cc. doses, thus saving the expense involved in house or office visits. Under these conditions it has been found to be practical and safe to see the patient once in 2 or 3 months for physical examination and blood count. Fourth, there is considerable saving to the physician and the dispensary because the smaller syringes and needles are less expensive than the larger ones used for the larger doses. Fifth, there is a large saving in time in the clinic patients since they are not required to undress for injections of the concentrated extracts—they can be made in the deltoid region instead of in the buttock.

A fairly comprehensive review of the literature in English, French, German and Italian leads us to suspect that the use of very concentrated (1-cc. dose) extracts is still not widespread. This seems to be due to the fear that the concentrated form lacks some substance which is contained in the less concentrated extracts. This hypothetical substance has been said to exert a beneficial, or at least a protective effect particularly on the neural lesions. It is not our experience that this medication (Reticulogen) is lacking in this protective factor, since nearly all of our patients have received as much benefit as could be expected from any extract. In those instances where more than one extract have been used the results have been as good in this respect with the very concentrated medication as with the more dilute types.

Summary. 1. Forty cases of pernicious anemia have been treated with a very concentrated form of liver extract—"Reticulogen."

2. Thirty-five have been followed for periods of from 2 to 4 years.

3. Control cases who have been kept on a less concentrated form of extract have been followed over the same period.

4. Further control is offered by the fact that 12 of these 40 cases had been previously treated with oral preparations and 12 had been treated with a less concentrated form of intramuscular liver extract.

5. Red blood cell and hemoglobin levels have been maintained at satisfactory figures.

6. Neural symptoms and signs have been controlled or actually improved in a vast majority of cases.

7. Patients have been able to continue work in most instances,

* Exact information as to cost of these medications is furnished in tables.

and in others, incapacitated persons have been returned to their occupations.

8. Evidence is submitted that patients under this form of therapy are able to combat successfully many types of acute and chronic disease almost as effectively as the average population.

9. The cost of this preparation is not prohibitive, and certain savings can be made because it is more easily administered than the less concentrated preparations.

Our thanks are offered to the technical staff of the hematology laboratory for their cooperation.

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THE VIABILITY OF THE SPIROCHETES OF SYPHILIS AND YAWS IN DESICCATED BLOOD SERUM.*†

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In both civil and military medical practice, transfusions are being made to an increasing extent with refrigerated whole blood and with

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blood serum or plasma which has been stored in the liquid or desiccated state. Since, under conditions of emergency, it may not always be possible carefully to select blood donors with respect to their freedom from syphilis, experiments were designed to determine the probable limits of safety, as regards the transmission of syphilis, in the use of such material for transfusion.

In a previous paper,¹² experiments dealing with the duration of infectivity of *Treponema pallidum* in citrated whole blood stored under conditions obtaining in blood banks were reported. In those experiments, an emulsion of virulent *T. pallidum* was added to either human or rabbit blood, and the blood stored at 2 to 4° C. Rabbits were inoculated with portions of the mixture before and at various intervals after refrigeration. Animals inoculated immediately and after 12 hours' refrigeration of the mixture, developed typical syphilitic lesions. In rabbits inoculated at 24 and 48 hours, the incubation period of the disease was prolonged, and some animals escaped infection. Animals inoculated at 72 hours and later were not infected. In a somewhat similar experiment, Bloch² obtained an infection at 72 hours but not later. From those experiments the conclusions were drawn that under conditions obtaining in blood banks, *T. pallidum* undergoes progressive deterioration during the storage period; that there is a corresponding reduction in the risk of transmitting syphilis by transfusion; and that it is probable that blood stored for 4 days or longer, even though taken from a syphilitic donor, can no longer transmit this disease.

The present paper is concerned with the infectivity of *T. pallidum* and *T. pertenue* in blood serum after freezing and desiccation. In brief, the experiments indicate that these organisms do not survive the drying process.

Preliminary Observations. Several years ago, the senior author noted that while *T. pallidum* would survive for long periods when stored in the frozen state at approximately -76° C., it commonly was promptly killed when desiccated from the frozen state.¹¹ In those studies, emulsions rich in treponemes were prepared from syphilitic lesions of the rabbit's testis. The emulsions were frozen rapidly in a solid carbon dioxide-alcohol mixture, and then desiccated according to the technique recommended by Swift¹⁰ and modified by Sawyer, Lloyd, and Kitchen,⁸ in which drying is carried out in a glass desiccator *in vacuo* in the presence of concentrated sulphuric acid.

More than 30 specimens from as many different sources were examined by dark-field after rehydration. In every instance, the spirochetes were badly distorted, apparently reduced in number, and none was motile. The infectivity for rabbits of 10 specimens was tested both before and after freezing and desiccation. The animals inoculated with the fresh material developed typical syphilitic lesions within the usual incubation period of the experimental disease. Nine of

the 10 specimens inoculated at various intervals after freezing and drying produced no lesions in the inoculated rabbits. One specimen tested 24 hours after the beginning of desiccation proved to be infective for 2 rabbits, although the incubation period of the experimental disease in these animals was much prolonged. Since that was the only instance, in both these and subsequent experiments, in which survival of treponemes was noted, this exceptional result is attributed to incomplete dehydration of the specimen within the 24-hour drying period. One other specimen tested after 24 hours' desiccation was non-infective for rabbits.

Recent Experiments. The preliminary experiments cited above were made for the purpose of finding a method of preserving the virulence of spirochetes *in vitro*. When it was obvious that freezing and drying did not provide a practical method for accomplishing this end, additional evidence regarding the non-infectivity of the material was not sought. The present experiments were carried out more meticulously, in a manner calculated to give the spirochete the best chance of survival.

Experimental Methods. The experiments were made at two different times, in the spring and in the fall of 1940. Except for minor variations, the procedure was the same for each experiment. Normal adult male rabbits were inoculated in each testis with the Nichols strain of *T. pallidum*. When a syphilitic orchitis was fully developed, the testes were removed and used in the preparation of the test material.* The day on which the desiccation was to be begun, each source animal was bled about 60 cc. from the heart. The blood was defibrinated, centrifuged, and the serum used for preparation of the mixture. The excised testes of each rabbit were emulsified in a mortar with sand with an amount of serum from the same animal equal to the weight of the two testes. This mixture was centrifuged nightly in order to throw down the gross tissue particles, and the supernatant fluid was used as the test material. This was always rich in actively motile *T. pallidum*. About 1 cc. of the supernatant was set aside for subsequent inoculation, and the remainder carried through the freezing and drying process.

Desiccation of the serum-spirochete mixture was carried out under the direction of one of us (J. H. B.) by the method described by Bauer and Pickels.¹ Approximately 5 to 6 cc. amounts were distributed into 50 cc. cylindrical vials with long narrow necks. The vials were then placed on their sides in a bath containing carbon dioxide ice and alcohol, and spun on their long axis in such a manner that the fluid inside froze in a thin layer on the sides of the vial. While the vials were still at the temperature of the solid carbon dioxide-alcohol bath, they were attached to a high vacuum line and lowered into a cabinet, the temperature of which was maintained at -18°C . Water was removed from the material rapidly, so that it appeared to be dry within a few moments. The tubes remained attached to the vacuum line for 60 hours, during which time the moisture in the vacuum system was removed by means of a special chamber held at -70°C . The cold trap was then removed, and drying continued *in vacuo* for 24 hours longer by introducing into the system a receptacle containing phosphorus

* The preparation of the test emulsion, the freezing and drying procedures, and the inoculation of the control animals were carried out in New York. Other phases of the experiments, including the long-term observation of animals, were carried out in Baltimore.

pentoxide. The pressure in the apparatus fell rapidly to 5 to 10 microns of mercury at the beginning of desiccation, and eventually reached a pressure of 0.5 micron of mercury. These procedures are believed to promote a high degree of dehydration. After drying was completed, nitrogen dried with calcium sulphide was allowed to flow into the vials, and the necks of the vials were sealed off with a flame. Subsequently, except for about 4 hours during which the vials were in transit, they were kept at refrigerator temperature until used. In the first experiment, the material was dried with the cold trap for 24 hours, and for 24 hours with phosphorus pentoxide.

TABLE 1.—INFECTIVITY OF *T. pallidum* IN RABBIT BLOOD SERUM BEFORE AND 3 DAYS AFTER DESICCATION.

Source of material:	Results of inoculation of fresh material intratesticularly and intracutaneously.				Results of inoculation of desiccated material intratesticularly, intracutaneously and intraperitoneally.			
Rabbit No.	Rabbit No.	Total amount of inoculum, cc.	Results.	Incubation period in days.	Rabbit No.	Total amount of inoculum, cc.	Results.	Results of lymph node transfer.
9-79	1	0.4	Pos.	13	13	3.0	Neg.	Neg.
					14	3.0	"	"
9-81	2	0.4	"	41	15	2.5	"	"
					16	2.5	"	"
10-01	3	0.4	"	13	17	4.0	"*	"
					18	4.0	"	Neg.

* Died in 23 days.

After the vials containing the test material had been frozen and attached to the drying apparatus, a control animal was inoculated with portions of each specimen which had not been frozen and dried. In the first experiment, each control animal was inoculated in the right testis with 0.2 cc. of fresh material, and intracutaneously on the back with 0.1 cc. at each of two sites. In the second experiment, control animals were inoculated in the testis with only 0.1 cc. intracutaneously at only one site. Dark-field examinations of the fresh material after the inoculations were completed showed numerous actively motile treponemes in each specimen.

The infectivity of the dried specimens was tested in the first experiment 3 days after desiccation was started and 5 days after, in the second experiment. The dried material was rehydrated to its original volume by the addition of sterile distilled water. Each specimen was then examined carefully under the dark-field microscope. The entire amount of material from one source animal was divided into two equal portions, and each inoculated into one test animal. In the first experiment, 0.5 cc. was inoculated into one testis, 0.2 cc. intracutaneously at two sites on the back, and the remainder injected intraperitoneally. In the second experiment, the same procedure was followed except 0.2 cc. was inoculated at each of 12 sites on the back.

The test animals were examined at least twice weekly for testicular, skin, bone, and eye lesions for a period of 90 days. At the end of this period, the

popliteal nodes from each pair of animals were removed, pooled, and injected into one testis of each of two normal rabbits which, in turn, were observed in a similar manner for 90 days. Three rabbits inoculated with desiccated material died before the end of the 90-day observation period, at 23, 21, and 75 days, respectively. All were without lesions suggestive of syphilis. The popliteal nodes of the latter two were transferred, within a few hours after death, to normal rabbits which likewise remained negative.

The experiments with *T. pertenue* were carried out in an identical manner to those just described. A strain of *yaws spirochetes* (strain YC) isolated by the senior author in Jamaica was used throughout.

TABLE 2.—INFECTIVITY OF *T. pallidum* IN RABBIT BLOOD SERUM BEFORE AND 5 DAYS AFTER DESICCATION.

Source of material:	Results of inoculation of fresh material intratesticularly and intracutaneously.				Results of inoculation of desiccated material intratesticularly, intracutaneously and intraperitoneally.			
Rabbit No.	Rabbit No.	Total amount of inoculum, cc.	Results.	Incubation period in days.	Rabbit No.	Total amount of inoculum, cc.	Results.	Results of lymph node transfer.
10-31	4	0.2	Pos.	14	19	13.0	Neg	Neg.
					20	13.0	"	"
10-32	5	0.2	"	17	21	12.0	"*	"
					22	12.0	"	"
10-33	6	0.2	"	18	23	7.5	"†	"
					24	7.5	"	"
10-51	7	0.2	"	13	25	6.0	"	"
					26	6.0	"	"
10-53	8	0.2	"	27	27	7.5	"	"
					28	7.5	"	"
10-55	9	0.2	"	14	29	10.0	"	"
					30	10.0	"	"

* Died in 21 days.

† Died in 75 days.

Results. *T. pallidum*. The protocols of these experiments are shown in Tables 1 and 2. In each instance animals inoculated with fresh material which had not been desiccated developed typical syphilitic lesions of the testis and skin within the usual incubation period of the disease. *T. pallidum* was demonstrated in the lesions of each animal. In most of the rabbits, the incubation period was unusually short, indicating that the test material was highly potent.

No animal inoculated with desiccated material developed any evidence of syphilitic infection despite the fact that each was

0 injected with from 6 to 65 times the dose given the control animals. That symptomless infection did not occur is indicated by the fact that the lymph nodes of the inoculated animals were not infectious for normal rabbits. Two rabbits (Nos. 24 and 25) developed small erythematous lesions at the sites of intracutaneous inoculation. Careful study of these by dark-field examination and by transfer of the lesions to normal rabbits failed to reveal *T. pallidum*. Since the testis of these animals remained negative, and subsequent lymph node transfer was negative, the lesions were regarded as non-syphilitic in origin.

Dark-field microscopic examination of the rehydrated material showed that many of the treponemes were badly distorted, being shriveled in appearance with the spirals quite irregular, in contrast to the regular configuration of fresh *T. pallidum*. It is of interest, however, that in each specimen there were some fairly normal-looking treponemes, and in several specimens approximately one-third of the spirochetes appeared not to have been appreciably altered in their morphologic characteristics. None was motile. There seemed to be some decrease in the number of treponemes in each rehydrated specimen as compared with the same specimen before desiccation. Since no actual counts were made, this point cannot be definitely established. Perhaps some organisms were distorted or fragmented beyond recognition.

TABLE 3.—INFECTIVITY OF *T. pertenue* IN RABBIT BLOOD SERUM BEFORE AND AFTER DESICCATION.

Source of material:	Results of inoculation of fresh material intratesticularly and intracutaneously.				Results of inoculation of desiccated material intratesticularly, intracutaneously and intraperitoneally.				
	Rabbit No.	Total amount of inoculum, cc.	Results.	Incubation period in days.	Days after desiccation started.	Rabbit No.	Total amount of inoculum, cc.	Results.	Results of lymph node transfer.
9-47	10	0.4	Pos.	47	3	31	3.5	Neg.	Neg.
					3	32	3.5	"	"
10-36	11	0.2	"	29	5	33	5.0	"	"
					5	34	5.0	"	"
10-37	12	0.2	"	35	5	35	5.5	"	"
					5	36	5.5	"	"

T. pertenue. Only a few observations on the effect of desiccation on *T. pertenue* were made, but the results are similar to those obtained with *T. pallidum* (Table 3). As is usually the case, the incubation period of the experimental disease in rabbits tended to

be longer than that observed in experimental syphilis. The lesions produced in the testis by the fresh material were typical of yaws and were dark-field positive for treponemes. No animal inoculated with rehydrated material developed any lesion suggestive of yaws, and the popliteal lymph nodes of the test animals, transferred after 90 days, failed to produce lesions in normal rabbits. As shown by dark-field microscopic examination, many of the treponemes in the rehydrated material were distorted, and none was motile. Some spirochetes were normal in appearance.

Discussion. Methods for the desiccation of biologic products, described many years ago by Martin⁷ and by Shackel,⁹ have undergone successive improvements at the hands of a number of workers.^{2-6,8} The method of desiccation employed in these studies is such that many species of bacteria and filtrable viruses can be dried with only slight, if any, loss of titre. There was, nevertheless, no evidence that the spirochetes of syphilis or of yaws survived this process. The test material was rich in treponemes, and its infectivity for rabbits was high before desiccation. The spirochetes were suspended in the tissue juices and serum of the animal from which the treponemes were derived, and desiccation was begun within a short time after the source material had been removed from the animal. Three to 5 days after the beginning of desiccation, large quantities of this rehydrated spirochete-containing material were injected into normal rabbits with completely negative results.

There is no evidence to suggest that *T. pallidum* or *T. pertenue* in the human host differs materially, from the standpoint of their resistance or susceptibility to desiccation, from the strains employed in these experiments. It seems fair to assume, therefore, that *T. pallidum* and *T. pertenue* occurring naturally in human serum or plasma would likewise be killed by desiccation, and that such material would be free from the risk of transmitting syphilis, even though the donor was in an active stage of the disease. To be sure, it would not be desirable knowingly to use blood from such persons, but even when great care is exercised in eliminating syphilitic donors, this cannot always be done with certainty. Moreover, in time of emergency or under stress of active warfare, it may not be possible carefully to select donors with respect to the presence or absence of syphilis or yaws. In the use of desiccated blood serum, the risk of transmitting syphilis or yaws is probably negligible.

Summary. 1. In experiments made several years ago, testicular emulsions rich in *T. pallidum* were frozen and desiccated. Upon rehydration, most of the spirochetes were distorted and 9 of 10 specimens tested failed to produce lesions when inoculated into normal rabbits. One specimen tested 24 hours after drying was begun produced lesions after a long incubation period. This result is attributed to incomplete dehydration of the specimen.

2. In recent experiments, the infectivity of virulent *T. pallidum* suspended in rabbit serum was tested before and 3 to 5 days after desiccation. Material from each of 9 specimens produced lesions in rabbits before desiccation. Three to 5 days after freezing and drying in an efficient desiccating apparatus, rabbits were inoculated with from 6 to 65 times the amount used for the control animals. None of 18 rabbits inoculated with desiccated material developed a syphilitic lesion, and their lymph nodes were not infectious for normal rabbits.

3. Of 6 rabbits similarly inoculated with desiccated *T. pertenue* from 3 different sources, none developed lesions, and their lymph nodes were not infectious for normal rabbits.

Conclusions. *T. pallidum* and probably *T. pertenue* are commonly killed by the process of freezing and desiccation, even when the method is such that the viability of many other bacteria and viruses is retained. Transfusion of desiccated blood serum or plasma is, therefore, probably without risk as regards the transmission of syphilis or yaws, even though the material be obtained from an infected donor.

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AN AUTOPSY SURVEY OF GASTRO-DUODENAL ULCERS IN THE PHILADELPHIA GENERAL HOSPITAL 1920-1937.*

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IN past years there has been much discussion in the literature of the incidence of peptic ulcer. Over a long period, many studies have been made, without conclusive results. The lack of agreement as to the incidence of peptic ulcer is largely due to two important factors: 1, the geographic factor (Table 1), and 2, the lack of

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uniformity of method used in conducting such surveys. As a result we have encountered considerable variation in the reported figures for the total incidence of peptic ulcers as found in autopsy material. In Table 1 it may be seen that, with the exception of Grunfeld's exceedingly high percentage and Lebert's low figures based on only 200 autopsies, the reported incidence ranges from about 1% to 5%. In Bassler's¹ study of 59,450 autopsies, the largest series of autopsies cited in the literature, the incidence was 4.4%. One of

TABLE 1.—THE INCIDENCE OF PEPTIC ULCERS.

Author.	Year.	Place of observation.	No. of cases.	% of ulcers.
1. Brinton ³	1859	London	5 00
2. Leube ³	1871	Germany	13,605	4 80
3. Ziemssen ¹⁶	1871	Leipzig	4.55
4. Lebert ⁷	1876	Germany	200	0 50
5. Grunfeld ⁶	1882	Europe	20 00
6. Berthold ²	1883	Germany	2 70
7. Welch ¹⁵	1894	United States	32,052	5 00
8. Nolte ¹¹	1900	Germany	...	1 23
9. Fenwick ⁵	1900	United States	47,912	4.20
10. Dreschfeld ⁴	1907	Baltimore, Md.	1,000	0 90
11. Stahl ¹³	1907	Germany	...	2 16
12. Lockwood ⁹	1913	United States	19,315	1.23
13. Bassler ¹	1926	United States	59,450	4 40
14. Sturtevant and Shapiro ¹⁴	1926	New York City	7,700	2 13
15. Muller ¹⁰	1934	United States	2 11
16. Portis and Jaffe ¹²	1937	Chicago	9,171	4 90
17. Gordon and Manning	1941	Philadelphia	22,956	2 75

Average (excluding Grunfeld's data) 3.10

TABLE 2.—DISTRIBUTION OF THE FOUR MAIN GROUPS ACCORDING TO AGE AND SEX.

Age.	Acute gastric.				Chronic gastric.				Acute duodenal.				Chronic duodenal			
	Male.		Female.		Male.		Female.		Male.		Female.		Male.		Female.	
	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
0-10	1	1.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10-20	1	1.2	0	0	0	0	0	0	1	1.2	0	0	0	0	0	0
20-30	0	0	2	5.4	1	1.7	0	0	2	2.3	2	5.9	0	0	0	0
30-40	7	8.3	2	5.4	5	7.9	1	3.6	10	11.6	1	2.9	4	11.1	1	16.7
40-50	22	26.0	4	10.4	10	16.8	4	14.3	17	19.8	7	20.5	8	22.3	0	0
50-60	21	24.5	5	13.5	14	22.3	7	25.0	12	13.9	3	8.8	7	19.4	1	16.7
60-70	16	18.7	9	24.4	19	30.2	7	25.0	21	24.5	10	29.4	6	16.7	0	0
70-80	13	15.2	12	32.5	9	14.2	5	17.8	18	21.0	6	17.6	10	27.8	2	33.3
80-90	4	4.7	2	5.4	5	7.9	4	14.3	5	5.8	4	11.8	1	2.8	2	33.3
Over 90	0	0	1	2.7	0	0	0	0	0	0	1	2.9	0	0	0	0
Totals	85		37		63		28		86		34		36		6	

Colored Patients.

Age.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
0-10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10-20	0	0	1	3.6	1	4.7	0	0	0	0	0	0	0	0	0	0
20-30	2	4.2	4	12.9	0	0	1	14.3	3	15.8	5	27.7	1	16.7	0	0
30-40	10	20.8	2	6.4	4	19.0	1	14.3	5	26.3	2	11.1	2	33.3	3	30.0
40-50	16	33.3	6	19.4	7	33.3	1	14.3	6	47.3	3	16.7	2	33.3	2	20.0
50-60	12	25.0	6	19.4	4	19.0	2	28.6	2	10.5	2	11.1	1	16.7	4	40.0
60-70	4	8.3	4	12.9	5	23.8	2	28.6	2	10.5	3	16.7	0	0	0	0
70-80	4	8.3	5	16.1	0	0	0	0	1	5.3	2	11.1	0	0	1	10.0
80-90	0	0	3	10.3	0	0	0	0	0	0	0	0	0	0	0	0
Over 90	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Totals	48		31		21		7		19		18		6		10	

the more recent and complete studies done in this country was that of Sturtevant and Shapiro¹⁴ from Bellevue Hospital, New York City, in which they found ulcers in 2.13% of 7700 autopsies.

From our review of the literature we have arrived at the belief that there is no "true" incidence for peptic lesions the world over. It would seem, and we shall show this to be true in part, that there is considerable variation in the incidence of ulcers with the years, at least in the area about Philadelphia, as well as with the geographic location of the study.

In an effort to supply data for the Philadelphia region, we have undertaken an analysis of the consecutive autopsies performed at the Philadelphia General Hospital for the 17-year period, 1920-1937. These data were gathered to be used in a study being conducted by the Fourth Conference of the International Society for Geographic Pathology. However, due to world conditions, the conference scheduled in Rome for June, 1940, was never held.

There are several factors peculiar to this study. The most important is the nature of the cases which come into the Philadelphia General Hospital, which is a municipal, charity institution. Many of the cases are extremely ill or moribund when admitted, making complete study impossible before death. Furthermore, as the nature of the institution considerably limits the use of special studies, not all the data which might be desired could be obtained for each case. The economic status of the patients which enter this institution is also low, hence the figures obtained from this study cannot be interpreted as being representative of a true cross-section of the population.

To complete these data we have surveyed the autopsy reports from the files of the hospital. It is important to realize that the information contained therein was compiled by various pathologists who used different terminology and criteria. Therefore, the personal element is large. However, there were available descriptions of the lesions in each instance, and we have used the reports of the autopsies, along with what clinical reports were available, in order to gain the fullest possible information about each case.

We have divided the lesions according to their location in the stomach and in the duodenum. The lesions have also been classified as acute and chronic. In all instances this latter distinction was made upon microscopic examination.

Between 1920 and 1937, 22,956 autopsies were performed at this hospital, and in this series 548 cases were found to show peptic lesions, an incidence of 2.75% for the entire series.

Table 2, presenting the age and sex distribution of lesions in both whites and negroes, has been subdivided into acute and chronic lesions in the stomach and in the duodenum. Peaks in the incidence of peptic lesions are seen in the fifth and seventh decades, the highest peak being seen in the latter decade (Charts 2a and 2b). In the

negroes, for both gastric and duodenal lesions, the peak for males is in the fifth decade, and for females, in the seventh. Part of this 20-year difference between races may be explained by the inexactness with which colored people state their age.

Chart 1 is a representation of the age distribution of peptic lesions of all types for both white and colored patients. It is to be noted that the peak of the incidence for colored patients appears about 20 years before that for white patients. This is in close relation to the average life-expectancy difference between the two races.

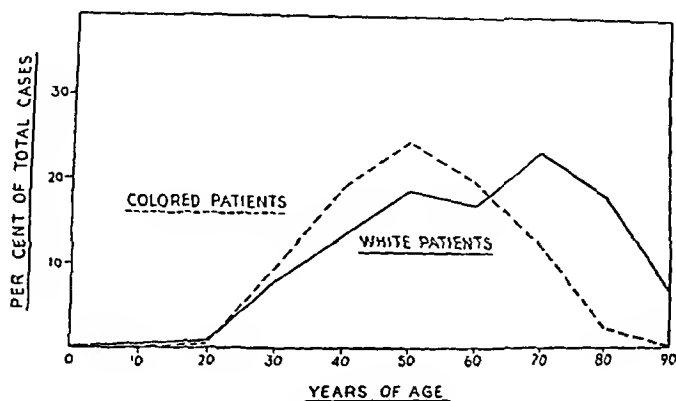


CHART 1.—Age-race distributions of peptic ulcers in 548 cases.

Table 3, analyzing the cases according to sex, race and type of lesion, shows that the ratio of colored to white is about 1 to 2.4. The hospital autopsy records give an average ratio of colored to white of 1 to 2.6. This is a significant indication that there is no racial factor operating in gastro-duodenal ulcerations in the Philadelphia region.

In this same table, the ratio between males and females is 2.1 to 1 for all types of peptic lesions. The ratio of males to females, duodenal lesions only, is 2.49 to 1, not significantly different from the ratio of all lesions. It would appear from this that the frequency of peptic lesions is twice as great in males, and that this frequency does not vary greatly with the years studied.

Table 4 was constructed for type of lesion, sex and the year in which the autopsy was performed in the hospital. We have divided the cases occurring before and after January, 1933, as we found that there was a significant difference in the occurrence of gastro-duodenal lesions before and after this date. The standard deviation for the figures found before 1933 is 0.49%; the standard deviation for those after 1933 is 0.59%. The probability that two such different groups could be drawn by chance from a homologous sampling of cases is considerably less than 1 in 100. We wish to call attention to the fact that the years 1920-1932 were within the period during which

prohibition of the sale of alcohol existed in the United States. The period 1933-1937 was without this prohibition. The significance of this fact cannot be determined accurately since records of alcoholism in the cases studied were very incomplete. It must also

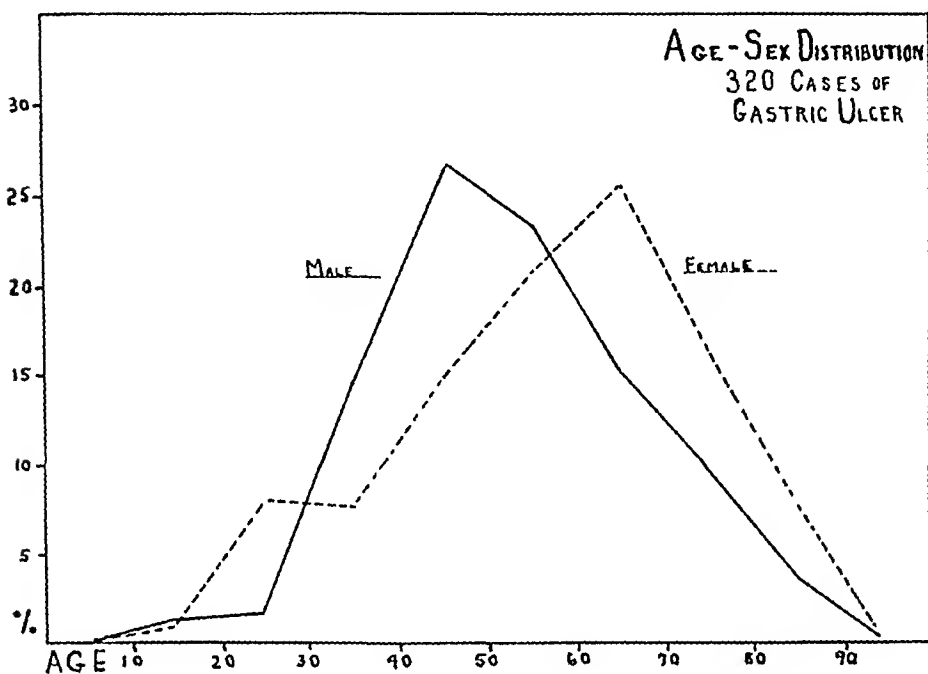


CHART 2a.

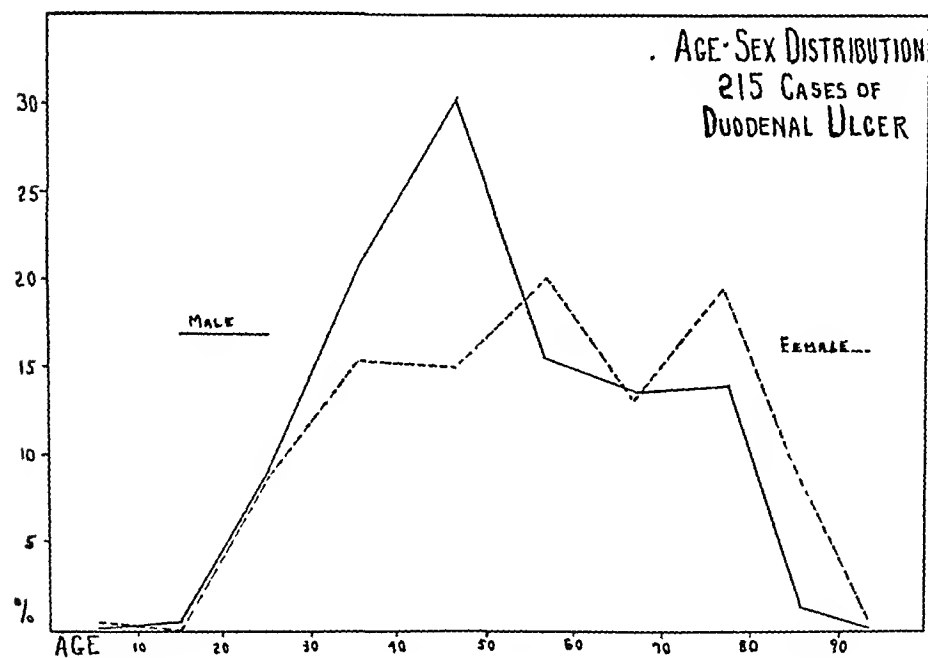


CHART 2b.

be remembered that this same period was one of economic insecurity and depression. Chart 3 illustrates clearly the difference between the period before 1933 and that after 1933. During this time there was no change in autopsy procedures or in the type of records available which might account for this difference.

TABLE 3.—SEX-RACE-LESION DISTRIBUTION.

	Acute gastric.	Chronic gastric.	Acute duodenal.	Chronic duodenal.	Total.	%.
White males . . .	86	60	90	36	272	49.9
White females . . .	44	32	28	6	110	20.2
Black males . . .	50	17	23	8	98	18.0
Black females . . .	29	7	20	9	65	11.9

TABLE 4.—ANNUAL SEX AND LESION DISTRIBUTION.

1920-1932.

Year.	Acute gastric.		Chronic gastric.		Acute duodenal.		Chronic duodenal.		% total autopsies for year.
	Male.	Female.	Male.	Female.	Male.	Female.	Male.	Female.	
1920	0	0	0	1	0	0	0	0	0.23
1921	4	2	3	3	5	0	0	0	2.35
1922	2	0	1	1	1	3	0	2	1.16
1923	3	3	3	1	1	2	4	0	1.64
1924	6	3	5	2	3	1	0	2	2.00
1925	3	1	1	2	6	1	0	0	1.44
1926	7	2	4	1	5	1	0	2	2.01
1927	4	0	0	1	7	1	2	0	1.18
1928	9	4	1	0	5	1	0	0	1.65
1929	7	4	2	0	1	2	0	0	1.42
1930	5	4	1	2	5	2	2	1	1.94
1931	8	4	2	2	2	5	1	0	1.92
1932	8	7	6	3	6	4	1	2	2.90

Average number of cases per year: male, 11.7; female, 6.6. Average % of total autopsies for a year: 1.68.

1933-1937.

1933	12	7	8	5	13	6	6	1	3.40
1934	16	3	7	2	19	5	3	0	2.85
1935	12	4	7	2	10	7	5	2	2.50
1936	13	10	15	5	13	6	5	2	3.50
1937	19	13	12	6	12	2	14	3	4.15

Average number of cases per year: male, 44.2; female, 18.2. Average % of total autopsies for a year: 3.28.

TABLE 5.—LOCATION OF LESIONS.

	Acute gastric.	Chronic gastric.	Acute duodenal.	Chronic duodenal.	Totals.	%.
Near esophagus . . .	4	3	7	1.3
Cardia	37	9	46	8.5
Fundus	64	18	82	15.3
Within 6 cm. of pylorus . .	71	34	105	19.7
At pylorus	45	27	72	13.5
Duodenum: First portion	140	47	187	35.0
Second portion	12	4	16	2.9
Third portion	6	3	9	1.7
More than one lesion in stomach	77	30	20	5	132	24.7
More than one lesion in duodenum	17	6	51	8	82	15.3

In Table 5 the lesions were arranged according to their acute and chronic nature, and according to their location in the gastro-intestinal tract. The stomach has been divided into five portions:

1. Near the esophagus: an area which was considered to be within 2 cm. of the esophageal opening into the stomach.
2. Cardia: the upper one-third of the stomach.
3. Fundus: the portion of the stomach from below the "cardia" to within 6 cm. of the pyloric ring.
4. An area within 6 cm. of the pylorus, limited distally by the pyloric ring.

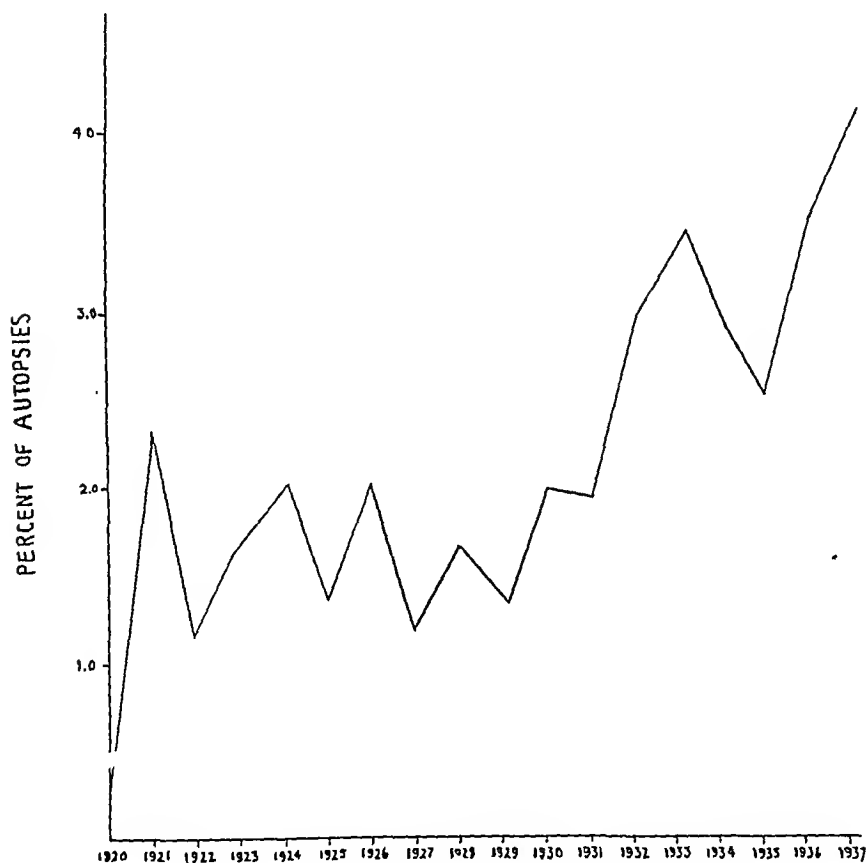


CHART 3.—Yearly distribution of peptic ulcers.

5. Pylorus: the region of the pyloric sphincter muscle and as far as the proximal edge of the duodenum.

The duodenum was divided into three portions:

1. First portion: the superior 2 inches (5 cm.).
2. Second portion: the descending portion, about 3 inches (7.5 cm.) long.
3. Third portion: in which was included the anatomic third and fourth portions, the last 5 inches (12.5 cm.) of the duodenum.

This latter inclusion of the two anatomic areas into one group was made because of the extreme rarity of lesions in this general area. The figures show that in the stomach region 83.5% of the lesions were within 6 cm. of, or at, the pylorus. In the duodenum, 88% of the lesions were in the first 2 inches (5 cm.) of the organ. This table does not include all of the 548 cases because specific information as to the location of the lesions was not available in every case.

If one desires to examine these results in terms of the three more usual divisions of the stomach, it may be done by adding the esophageal and cardiac areas, yielding 9.8%, this corresponding to the "Cardia." The "Fundus" is the same as seen in our table. The "Pylorus" amounts to the sum of the area 6 cm. away from the pyloric ring, and the pyloric ring, 33.2%. Also in Table 5 have been included figures to show the number of cases in which there occurred more than one lesion in either the stomach or duodenum. It was found that 4.7% of the gastric lesions were accompanied by other peptic lesions in the duodenum, and 4.3% of the duodenal lesions showed concomitant lesions in the stomach. The size of the ulcer was the determining factor in arriving at which lesion was of primary importance.

Because liver lesions were noted in an extremely high percentage of this series of autopsies, Table 6 was constructed to bring out this fact. Liver lesions being rather difficult to define, arbitrary division as to the degree of altered function was undertaken. "Parenchymal Degeneration" is a term variously used by the group of men performing the autopsies. Many of these cases can best be considered as terminal or postmortem change that has little importance in regard to liver function during life. In the group "Metastatic Carcinoma" have been included cases in which islands of definite malignant tissue were proven by microscopy. The amount of dysfunction that such a condition presents probably belongs with the "Chronic Passive Congestion" group in degree. Cardiac lesions being present in a large percentage of these cases, the liver categories were divided into those with, and those without, cardiac lesions. This table shows that 58% of ulcer cases were accompanied by definite liver damage. A random sampling of the autopsies at the same hospital without regard to peptic lesions showed 35% with definite liver damage. The standard error of each of these figures is about 2%. The difference between the ulcer group and the control group is 11 times the standard error. The chance of obtaining, from a homogeneous population by purely random sampling, two samples of this difference is incalculably small.

Nowhere in the literature have we found observation of this coexistence of peptic ulcer and liver damage. The relationship between liver function and peptic ulceration has not been clearly established. However, we suggest that liver damage may be a factor in altering the local circulation of the stomach and duodenum,

thereby predisposing to peptic ulceration. This fact is further suggested by the large number of cases of cardiac damage found in relation to peptic lesions.

TABLE 6.—ACCOMPANYING LIVER LESIONS.

	Acute gastric.	Chronic gastric.	Acute duodenal.	Chronic duodenal.	Totals.	%.
<i>Cirrhosis:</i>						
With cardiac lesion . . .	11	8	14	5	38	7.1
Without cardiac lesion . . .	12	3	9	2	26	4.8
<i>Chronic Passive Congestion or Necrosis:</i>						
With cardiac lesion . . .	52	12	30	10	104	19.4
Without cardiac lesion . . .	49	26	46	20	141	26.4
<i>Parenchymal Degeneration:</i>						
With cardiac lesion . . .	15	10	15	7	47	8.8
Without cardiac lesion . . .	45	26	34	14	119	22.2
<i>Normal Liver:</i>						
With cardiac lesion . . .	1	3	3	0	7	1.3
Without cardiac lesion . . .	4	5	7	1	17	3.2
<i>Melastatic Carcinoma:</i>						
With cardiac lesion . . .	1	2	0	1	4	0.8
Without cardiac lesion . . .	5	3	2	1	11	1.9

TABLE 7.—COMPLICATIONS OF PEPTIC ULCERATION.

	Acute gastric.	Chronic gastric.	Acute duodenal.	Chronic duodenal.	Total.	%.
Bleeding of ulcer	46	8	28	14	96	17.9
Perforation of ulcer	39	22	65	13	139	25.0
Mucosal scars	19	67	31	21	138	25.8
Probable malignancy of ulcer	6	0	0	0	6	1.1

The complications of peptic ulcer are dealt with in Table 7. Perforation occurred in 25% of the cases, and bleeding in 17.9%. The presence of mucosal scars is an indication of the healing tendency of ulcers. This was noted in 25.8% of this series. Also of note is the fact that histologic examination of the ulcers revealed but 6 cases in which there was any suggestion of malignancy in the ulcer base.

Summary. This study of 22,956 autopsies has shown peptic ulcers in 2.7% of the cases. There seems to be no racial difference in incidence between white and colored patients. Males show ulceration twice as frequently as females. There has been a significant increase in the observed incidence of ulcer since 1933. Liver lesions occur in ulcer cases in a significantly greater percentage of autopsies than in a random sample of this hospital's autopsy records. While the incidence of ulceration varies with the geographic locality and with the calendar years studied, the age groups most involved, namely the fifth to seventh decades, remain constant in our material.

We wish to express our sincere gratitude to Dr. M. M. Lieber for the use of his cross-index of the autopsy records of the Philadelphia General Hospital, and to thank Dr. J. H. Clark for making available these records.

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THE USE OF 2-SULFANILAMIDOPYRAZINE IN PNEUMOCOCCAL PNEUMONIA.

A PRELIMINARY REPORT.*

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DOMAGK'S³ discovery of the chemotherapeutic value of sulfanilamide has opened a new field of medicine. Subsequent investigations have broadened the usefulness of this type of therapy, largely through the development of other derivatives. Several thousand such compounds can be synthesized by introducing substituent groups in the molecule. Clinical use of a few of them has followed observations of their antibacterial activity and relative toxicity for animals. Thus, sulfapyridine and sulfathiazole have gained wide

* This study was aided by a grant in honor of Craig Yeiser.

acceptance as useful and relatively safe agents in pneumonia therapy. A third, sulfadiazine^{5,7} has shown promise of clinical usefulness in pneumococcal pneumonia. Still another derivative, 2-sulfanilamidopyrazine* ("sulfapyrazine"), is the subject of this study. It interested us particularly because of a previous observation that pyrazine monocarboxylic acid is less toxic than the corresponding pyridine carboxylic acid. As there have been no clinical reports published on the use of sulfapyrazine, we offer this brief preliminary study in hope that it will stimulate further trial.

2-Sulfanilamidopyrazine ("sulfapyrazine") is a colorless, tasteless, crystalline substance, melting at 255° to 257° C. It is slightly soluble in water, but dissolves readily in weakly alkaline solutions. Its sodium salt, sodium 2-sulfanilamidopyrazine monohydrate, is freely soluble and is less strongly alkaline than the sodium salts of sulfapyridine, sulfathiazole and sulfadiazine (pH 9.3, 10.7, 10.0, 10.2, respectively, for 10% solutions in physiologic saline).

Single doses of 1 gm. per kg. (as the sodium salt, but figured on the basis of the free drug) were injected intraperitoneally into mice. Death followed usually within 24 hours. Doses of 0.5 gm. or less per kilo of body weight were tolerated without ill-effects. Four dogs were given 2 gm. of the drug daily for 40 days. They not only tolerated these doses well but gained weight during the period of observation. Further observations indicate a low order of toxicity in rats, dogs and monkeys, and will be reported fully in another communication.

Single dose studies, employing 4 gm. by mouth per dose, were made on 6 convalescent hospital patients. Frequent determinations of the blood level disclosed the maximum between 4 and 8 hours after administration of the drug. No abnormal symptoms were detected when the drug was given to patients in amounts of 8 to 12 gm. daily for a short period of time. Following these observations, the drug was administered to 22 pneumonia patients, the responses of which form the basis of this report. Almost simultaneously with our editorial statement about its use in pneumonia,⁴ Raiziss reported that he had found sulfapyrazine effective against Type II pneumococcus infection in mice.⁶

The great majority of the patients had typical pneumonia, although a few had given atypical histories; all had unequivocal clinical or roentgenographic signs of consolidation. Because of the uncertainty concerning the efficacy of the drug, only those patients were selected who, on admission, did not seem to require intravenous therapeutic agents. All 22 patients recovered. Pertinent data concerning these patients are recorded in the table.

The drug was administered orally in each instance. An initial dose of 2 or 4 gm. was employed; thereafter, 1 gm. was given every

* This drug was synthesized and supplied by Dr. R. C. Ellingson of Mead Johnson & Co.

4 hours until the patient was free of fever for 2 days. Blood "sulfapyrazine" determinations were made at frequent intervals, employing the method of Bratton and Marshall.² As expected from preliminary observations, the level of the drug in the blood stream rarely was higher than 3 mg. per 100 cc. when the above dosage was employed; in several instances, recovery occurred when only traces were demonstrable in the blood. The drug rapidly disappeared from the blood after administration.

TABLE 1.—ANALYSIS OF PNEUMONIA CASES TREATED WITH SULFAPYRAZINE.

Sex.	Color.	Age.	Type.	Blood culture.	Dosage.		Highest level.	Lobe involved.	Day of disease.	Outcome.
					Grams.	Days.				
M	W	57	XXXII	Neg.	28	5	3 2	LL	2	Well
M	W	28	VII	Neg.	34	6	2 1	RU	3	Well
M	W	19	I	Neg.	28	5	Trace	RL	1	Well
M	C	21	XIV	Neg.	27	5	Trace	RL	3	Well
M	W	17	VII	Neg.	25	4	1 6	RL	3	Well
M	C	33	V	Neg.	23	5	Trace	LL	1	Well
M	C	27	VIII	Neg.	25	5	2 2	LL	1	Well
M	C	18	XXVII and "Carver"	Neg.	26	5	2 1	LL	5	Well
M	W	14	I	Pos.	27	5	2 3	LL	3	Well
M	C	39	III	Neg.	18	3	2 5	RM	6	Well
								RL		
M	C	54	VIII	Neg.	24	4	Trace	LL	1	Well
M	C	38	I	Neg.	12*	2	2 3	RU	3	Well
F	W	63	VIII	Pos.	45	7	2 9	RU	4	Well
F	W	34	II	Neg.	37	6	1 5	RL	3	Well
M	W	19	XXVII	Neg.	24	4	1.7	LL	3	Well
M	W	42	I	Neg.	45	8	2 9	LL	4	Well
F	W	29	VII	Neg.	14	3	1 7	LL	3	Well
F	W	17	V	Neg.	24	4	2 4	RL	4	Well
M	C	29	I	Neg.	34	6	2 5	RUM	4	Well
M	W	64	I	Neg.	26	4	3 5	RL	3	Well
F	C	17	V	Neg.	25	4	3 3	LL	3	Well
M	W	52	I	Pos.	29	4	4.6	RM	5	Well

* This patient's temperature had fallen to normal after 12 gm. of sulfapyrazine. At this time, he was inadvertently given sulfathiazole; consequently, therapy was continued with sulfathiazole.

Within 18 hours after the institution of treatment, all of the patients showed clinical improvement. In 4 instances, the diminution or disappearance of pleural pain was the first improvement noted subjectively; more often, improvement was general and less easily defined. In 12 of the patients, a critical fall of temperature occurred 12 to 24 hours following the administration of the first dose. In no instance was there a recrudescence of fever after the temperature had fallen below 100° F. (rectal). Three of the patients had positive blood cultures at the time treatment was begun; 18 hours later, blood cultures in media which had been enriched with

para-amino benzoic acid were sterile. None of the patients had purulent complications either before or after treatment.

Untoward reactions to the drug were infrequent, if present, in this series. No patient complained of nausea and none vomited. Mental symptoms were observed in 2 patients; these consisted of hallucinations and persecutory delusions occurring after 48 hours of treatment. Both improved rapidly after discontinuance of the drug and had no memory of the unpleasant incident. Subsequent administration of the drug in the same doses failed to duplicate this clinical picture of disorientation or hallucination. Daily examination of the cellular elements of the blood disclosed no apparent effects. Similarly, frequent examinations of the urine and urinary sediment did not reveal the presence of blood or evidence of depression of renal function. Skin rashes did not occur in this series.

Summary. A new derivative of sulfanilamide, 2-sulfanilamidopyrazine, has been given clinical trial in pneumococcal pneumonia. Twenty-two selected patients received the drug by mouth. All showed prompt improvement and ultimate recovery, with no significant signs of toxicity. The drug is apparently tolerated well and it deserves further clinical trial.

By the time the proof of this article was returned, the authors had treated 10 additional patients, of whom 2 were bacteremic. All recovered and had no signs of toxicity following the administration of sulfapyrazine.

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THE CAPILLARIES IN MYXEDEMA.

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THE heart in myxedema has been fully described by one of us^{2a-c} in 1918-19, and the symptomatology, which has been verified by many authors in the meantime, may be taken for granted. Less attention has been paid to the peripheral circulation in myxedema. Recently we have devoted ourselves to the study of the capillaries in connection with this disease. We have had the opportunity of

observing 8 myxedema patients, some of them for several years. They were all women, between 30 and 62 years of age.

We studied the capillaries of the ungual limbus previous to, during and subsequent to thyroidin treatment. In 7 of the 8 patients the capillaries showed a uniform characteristic picture. They were fewer in number and very narrow (Fig. I). In some instances there was only a barely recognizable, fine line to be seen in the microscopic field. Details, particularly a flow, could not be distinguished. In those places where the capillaries were not narrowed there was a brittle mass filling them, with a great many intervening gaps. In other places, only the small loop was seen, while the straight portions were invisible. In those instances in which the entire length of the capillary vessel was recognizable both limbs were in almost every case very straight with no tortuous or crooked portions. The two limbs were very close together and the intermediary part was pointed and sharply bent. The flow, as far as any was recognizable, was apparently rapid. The width of the venous and arterial part did not show much difference; sometimes none at all. In some cases the whole picture was somewhat hazy. It was as though the details were slightly veiled. Since the number of capillaries was small the intermediary spaces with no vessels were clearly visible. We give here the case history of one of the patients who was under our observation for 4 years.

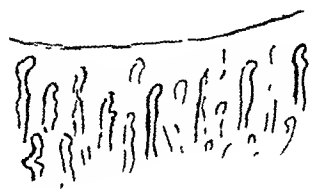
Case Report. Mrs. H., aged 33, weighed 67 kilos. She said that she had always been healthy, and had had 4 normal deliveries. Menstruation has always been regular without any trouble. Recently she has gained markedly in weight. Face and hands had become swollen, her movements strikingly slow. She was impressed by the fact that the housework became more and more difficult for her. Sometimes she had pains in the back and legs and a feeling of tightening and oppression in the region of the heart. Her voice had become lower and coarse. She, moreover, complained that she was continually cold and constipated. Physical examination: The patient is small and looks rather pasty. The skin is pale and also rough and cold to the touch. Judging by her face, she is older than would be expected for her age. The pharynx is without any abnormalities, the tongue is thick, the heart enlarged both right and left sides, the heart sounds are clear but extremely muffled, the pulse is regular, 56 per minute. Blood pressure 95/60 mm. Hg. On the screen, we saw that the action of the heart was slow and that the contractions were superficial. Lungs, normal. Abdomen, normal. The extremities are sensitive to pressure, the skin is rough, but there is no edema. The reflex responses are slow. The pupils react normally to light. Blood picture: hemoglobin, 82%; erythrocytes, 4,200,000; leukocytes, 5000. Basal metabolic rate, -29%. Blood cholestrol, 423 mg. per 100 cc. Sella turcica, without any peculiarities.

Similar findings were obtained in the other 6 patients. During thyroidin treatment the number of capillaries increased and their limbs became wider (Fig. II, a-c). While they had been straight previous to the treatment, they now became curved and tortuous. The venous portion was sometimes markedly distended and the bloodflow slowed down so that stagnation was brought about.

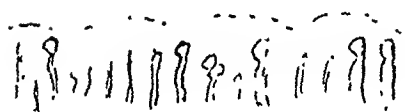
It is worthy of note that the changes of the capillary picture were by no means in proportion to the clinical improvement. In some instances the capillary picture varied in such a way that in some fingers wide capillaries were found while in others they were narrow. No parallelism between the decreasing circulation time and capillary dilation was noted (tested by means of a 20% magnesium sulphate injection). Although the bloodflow became more



Ia



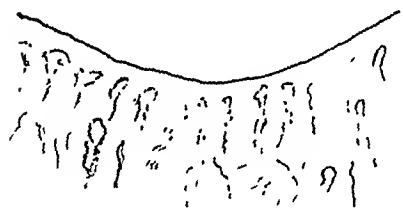
IIa



Ib



IIb



Ic



IIc

FIG. I

FIG. II

FIG. I.—Capillaries of the ungual limbus of 3 myxedema patients before thyroidin treatment.

FIG. II.—Capillaries of the ungual limbus of 3 myxedema patients after thyroidin treatment.

rapid, the capillaries, to begin with, often remained narrow. Only later did they become wider, but no regularity could be observed in this respect. Thus, for instance, in one of the patients, the capillaries were very narrow, while the circulation time was normal.

An explanation of this discrepancy might be that the circulation time does not depend exclusively on the capillary dilation, but is also linked to the condition of the arteriovenous anastomoses. Opening the arteriovenous anastomoses brings about considerable

increase of the circulatory speed without the cross-section of the capillary bed being considerably enlarged. This has also been verified by Michael's and Buschke's¹ investigations who found the capillaries to be surprisingly narrowed in Graves' disease, a condition similar to that observed by us in myxedema. Since, however, these two conditions are associated with the opposite circulatory symptoms, particularly as concerns the circulatory speed, it should be concluded that these symptoms are produced by the opposite behavior of the arteriovenous anastomoses, not, however, by that of the capillaries. It should be assumed that in Graves' disease with its abnormally increased oxygen requirement of the tissues and increased circulatory speed the arteriovenous anastomoses are open. In the myxedema patient with his reduced oxygen requirement in the tissues and reduced circulatory speed, the capillaries are certainly narrowed, but, in addition, the arteriovenous anastomoses must, as a consequence, also be closed. If, as the result of thyroidin treatment, the O_2 requirement rises again so that an increased blood supply of the tissues becomes necessary, this increase may be brought about by dilation of the capillaries as well as by the opening of the arteriovenous anastomoses. Both may, however, occur in interaction with one another. Thus it becomes comprehensible that the capillary picture is not always parallel to the increase of the circulatory speed.

The question as to whether the control of the peripheral portion of the circulation (capillaries, arteriovenous anastomoses) is executed by the thyroid hormone is not easily decided. Since, apparently, the arteriovenous anastomoses show an opposite action in Graves' disease and myxedema, it should be assumed that it is actually the thyroid hormone that is the responsible factor in this process. This would mean that the same hormone that on the one hand sets the circulatory machinery in motion, increases the number of its revolutions (the minute volume as well as the amount of blood in circulation) which shortly increases the actual work performed by the heart. On the other hand, this hormone must be held responsible for the less powerful action of the heart. That the capillary function might also be subject to the activity of the thyroid hormone, is highly improbable. This would also be contradictory to their uniform behavior in Graves' disease and myxedema.

It is a well-known fact that the cardiac muscle in myxedema contains much fluid matter (Zondek). Some of our patients who complained of angina-like heart trouble were improved by this therapy. The optimal dosage varied greatly as to the individual case (from 0.3 to 0.4 gm. thyroidin weekly up to 0.4 to 0.6 gm. daily). Up to the present, the stenocardiac symptoms occurring in the patients who are suffering from myxedema have been explained by their tendency to develop an early arteriosclerosis. It has been shown by animal experiments that thyroidectomy may induce severe

atheromatosis of the aorta (v. Eiselsberg, Pick and Pineles, *et al.*). The immediate response to thyroidin therapy in most cases, however, in itself supports the theory that these troubles cannot be due to arteriosclerosis. It is, in our opinion, more rational to assume that the process of swelling taking place in the cardiac muscle with the resulting pressure on the blood-vessel—which means a reduced blood supply to the cardiac muscle—is also active in bringing about the stenocardiac symptoms. It is suggested that the same narrowing of the blood-vessels which was found on the peripheral capillaries takes place in the myocardium. In this way, the beneficial effect of thyroidin is also explained.

In any case the nature of the process taking place in the blood-vessels which induces the stenocardiac paroxysm in the myxedema patient is entirely different from that which is found in sclerotic changes of the blood-vessels. This is not only evidenced by the intensity of the symptoms, which do not attain the same degree in myxedema patients as they do in connection with genuine angina pectoris, but it is also made clear by the different response to thyroidin therapy. Recent investigations have produced much elucidation insofar as it is now evident that genuine angina pectoris, in particular the so-called angina of effort, is beneficially influenced by thyroidectomy. We are, therefore, considering two different phenomena of the cardiac—circulatory apparatus.

By the way, in those patients who present the symptoms of slight stenocardia, even if there are no other symptoms of myxedema, one should always consider the possibility that their troubles may be thyrogenous in nature (abortive type of myxedema heart) (Zondek.^{2a}). Particularly so, if the basal metabolic rate is lowered. In patients of this kind we occasionally found it reduced to as low as 30%. It was, however, striking that the values varied greatly. Small doses of thyroidin may now and then produce a surprisingly favorable result (0.3 to 0.4 gm.).

Summary. In 8 women suffering from myxedema with typical myxedema hearts, the peripheral circulatory portion was subjected to exact investigation. In 7 cases the capillaries (ungual limbus) were markedly changed, the most striking feature being pronounced narrowness of the limbs. In some instances the loops only were recognizable. The number of visible capillaries was reduced. On thyroidin administration, the capillary picture as well as the clinical symptoms and the circulation time gradually returned to normal. No parallelism, however, could be established between the behavior of the capillaries on the one hand, and the general condition and the acceleration of the circulation time on the other hand. In the light of this evidence, the conclusion may be drawn that thyroidin is active in opening the arteriovenous anastomoses. Apparently the cross-section of the anastomoses as well as that of the capillaries is

reduced in cases of myxedema, which is comprehensible in view of the abnormally reduced oxygen requirement.

In many cases myxedematous patients suffering from precordial pains similar to anginal states are likewise relieved by thyroidin administration. In this case, thyroidin is assumed to bring about a dehydration of the heart muscle (Zondek) and thus an increase in the blood supply of the heart. It is, therefore, suggested that the development of precordial pains in myxedematous patients is not, as a rule, due to sclerotic changes of the cardiac vessels, as generally assumed, but to mechanical impairment of the coronary flow.

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BOOK REVIEWS AND NOTICES

THE BRITISH ENCYCLOPEDIA OF MEDICAL PRACTICE Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. *Complete Index.* Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of the Royal College of Physicians of London. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., Professor of Medicine, University of London, etc., G. GREY TURNER, D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., Professor of Surgery, University of London, etc., JAMES YOUNG, D.S.O., M.D., F.R.C.S. (EDIN.), F.C.O.G., Professor of Obstetrics and Gynæcology, University of London, etc., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., Late Physician, Hospital for Tropical Diseases, London, and F. M. R. WALSHE, O.B.E., M.D., Sc.D., F.R.C.P., Physician in Charge of the Neurological Department, University College Hospital. Pp. 486. London: Butterworth & Co. (Publishers), Ltd., 1941. Price, \$10.00.

IN spite of the difficulties of producing an Index in England, under war-time conditions, the publishers have completed this important task in such a satisfactory way that the value of the whole set is considerably enhanced. In spite of the increased costs in paper, printing and binding, the Index is issued at a lower price than the other volumes. E. K.

THE MEDICAL ASPECT OF BOXING. By ERNST JOKL, M.D., Head of Department of Physical Education, Witwatersrand Technical College, Johannesburg, So. Africa; Consultant, Medical Aspect of Physical Education, S. A. Defense Force. Pp. 251; illustrated. Pretoria, So. Africa: J. L. Van Schaik, Ltd., 1941.

THIS monograph should be of great interest to all those connected with athletes and games of the "body contact" type. While boxing is primarily dealt with in this book, head injuries are frequent in football, or ice-hockey. Although the knock-out punch with its consequent concussion is delivered deliberately in boxing and is a hazard connected with that sport, nevertheless, a head injury is still a head injury regardless of how or in what field of athletic endeavor it is received.

"The most frequent knock-out is caused by blows to the chin, those coming somewhat from the side and from below (uppercuts) being rather more effective than blows from directly in front. They result in immediate loss of consciousness lasting for periods of variable length. From all available knowledge and experience, it is concluded that the typical knock-out blow to the chin leads to a two-phasic jerk, which affects the medullary centers. During the first phase the clivus and the anterior edge of the foramen magnum of the occipital bone are pushed against the lower portions of the pons and the upper anterior surface of the medulla oblongata; while during the second phase by virtue of a contrecoup (rebounding) effect, the medulla oblongata bounces back against the internal surface of the occipital bone and the posterior edge of the foramen magnum. It would appear that this double impact produces unconsciousness for injury to the medulla oblongata produces unconsciousness much more readily than does injury to any other part of the brain."

Although discussion of the immediate effects of a "blow sufficiently severe to produce concussion" is given, in subsequent chapters the remote sequelæ of repeated head injuries, headache, dizziness and instability in gait are described and the physiology discussed.

Other methods of knocking out an opponent by blows over the heart or solar plexus with their accompanying injuries to thoracic and abdominal organs are outlined. Each variety of injury is illustrated by case histories. A good bibliography is appended.

All in all the author develops a fairly grim case against any of the "bodily contact" sports. However, he does not have any suggestion either for improvement in the methods of conducting them or for substitution of different and possibly less dangerous types of sport. It is quite true that any of the injuries he describes can occur. But the Reviewer believes that even if these facts were carefully explained to him no real athlete would refuse to take part in such games on that account. The book is useful however in pointing out to those in charge of athletics the potential dangers concerned in any form of sport so that by careful supervision and observation of the participants repeated injuries can at least be minimized.

F. G.

THE HEART IN PREGNANCY AND THE CHILDBEARING AGE. By BURTON E. HAMILTON, M.D., Cardiologist (since 1921) to The Boston Lying-In Hospital, and K. JEFFERSON THOMSON, M.D., Associate Physician, Metropolitan Life Insurance Sanatorium, Mount McGregor, N. Y.; Research Associate in Medicine, Albany Medical College, etc. With a Section Entitled "Delivery and Obstetrical After-Care of Cardiacs," by FREDERICK C. IRVING, M.D., F.A.C.S., Professor of Obstetrics, Harvard Medical School; Obstetrician in Chief, The Boston Lying-In Hospital. Pp. 402; 33 illustrations. Boston: Little, Brown & Co., 1941. Price, \$5.00.

THE authors of this timely book very properly mention their considerable experience in the management of heart disease in young women. Of the three sections, the first deals with the diagnosis and treatment of pregnant women with heart disease; the second discusses the physiology of the circulation during pregnancy; the third describes the course of specific cardiovascular diseases throughout the childbearing age. Much is herein contained which could be found otherwise only by long personal experience and careful perusal of the periodical literature.

W. J.

FRACTURES AND OTHER BONE AND JOINT INJURIES. By R. WATSON-JONES, B.Sc., M.Ch.Orth., F.R.C.S., Civilian Consultant in Orthopaedic Surgery of the Royal Air Force, etc. Pp. 724; 1034 illustrations. Second Edition. Baltimore: The Williams & Wilkins Company, 1941. Price, \$13.50.

THE first edition of this work was published in January, 1939, and this second edition was published a year later. The first edition was written "in days of relative peace." Since then casualty surgery has become of such importance that the author has "rewritten the chapter on Open and Infected Fractures and War Wounds, and included recent developments in chemotherapy, blood and plasma transfusion, the treatment of wound shock, the closed plaster technique, and the technique of amputation."

The arrangement of this book is excellent and the illustrations are superb. The chapter on the Repair of Fractures, while short, is adequate and above all is clearly written so that even a student will not be confused

after reading it. The Reviewer is impressed with the repeated emphasis that is placed on adequate immobilization of fractured parts.

The sections on the treatment of open and infected wounds are well done. Exception will be taken by some to primary skin suture in any of the cases, even though chemotherapy is used as a prophylactic measure against infection. Fifteen grams of a sulfonamide seems a large amount to be utilized locally but others have used as much with very favorable results.

The final chapter deals with the organization of a Fracture Service and should prove very valuable in both civil and military practice. It is easy to understand why the first edition of this volume was exhausted before 12 months following its publication. The second edition will be equally well received for it is an unusually fine piece of work. I. R.

SYNOPSIS OF DISEASES OF THE HEART AND ARTERIES. By GEORGE R. HERRMANN, M.S., M.D., PH.D., F.A.C.P., Professor of Medicine, University of Texas; Director of the Cardiovascular Service, John Sealy Hospital; Consultant in Vascular Diseases, U. S. Marine Hospital. Pp. 468; 91 illustrations. Second Edition. St. Louis: The C. V. Mosby Company, 1941. Price, \$5.00.

THIS second edition is similar to the first in plan and content. By increasing the length by 124 pages, the author has been enabled to include a discussion of heart disease in relation to surgery and obstetrics, to enlarge the section on peripheral vascular diseases, and to add a chapter on military medicine. W. J.

CLINICAL ASPECTS OF THE ELECTROCARDIOGRAM Including the Cardiac Arrhythmias. By HAROLD E. B. PARDEE, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital; Consulting Cardiologist, Woman's and Methodist Hospitals; Attending Cardiologist, New York Polyclinic Medical School and Hospital. Pp. 434; 219 illustrations on 102 figures. Fourth Edition, revised. New York: Paul B. Hoeber, Inc., 1941. Price, \$5.75.

THIS book continues to be a unique and concise guide for the student who wishes to learn both the fundamentals of the electrocardiographic method and abnormalities of the electrocardiogram which may be encountered in clinical medicine. According to the Preface: "Since the publication of the last edition of this book the use of precordial leads has added greatly to the diagnostic value of the electrocardiogram." The use of precordial leads is accordingly discussed and illustrated. W. J.

BERKELEY MOYNIHAN, Surgeon. By DONALD BATEMAN. With a Preface by LORD MOYNIHAN. Pp. 354; illustrated. London: MacMillan & Co., Ltd., 1941. Price, \$4.00.

DURING the past year several biographies and autobiographies of famous surgeons have been published. Among the great technical surgeons of our time Moynihan ranks near the top. This is a simple story of his life and Dr. Bateman has avoided the accusation of hero-worship. Moynihan, the man and the surgeon, lives again in this volume. His rise from poverty to wealth, from an assistant house surgeon to the greatest surgeon in Britain reads like a tale of Horatio Alger. The volume covers not only his British associations, but throughout one finds references to American colleagues and American surgery.

With all the honors that were bestowed upon him in Britain and in this country, he, like many other eminent men, failed to be made a Fellow of the Royal Society. It was a great blow. One by one nearly every honor had come to him, but this one, which he wished above all others, was denied him and he became a bitter man. It was an unfortunate thing that he finally attacked the President of the Royal Society in a letter to the *Times*.

Dr. Bateman in a remarkably able fashion sets forth this great man's virtues and faults, his generosity and his selfishness. It should be read by all surgeons, many internists and by all those who are interested in the biography of illustrious men.

I. R.

ORBITAL TUMORS. By WALTER E. DANDY. Pp. 168; 100 illustrations. New York: Oskar Piest, 1941. Price, \$5.00.

THIS small book is a monograph in which the author presents his wide experience, covering a period of over 20 years, with orbital tumors. The material is presented in the form of 31 case reports accompanied by good photographs and excellent sketches.

In the summary and conclusions, the author stresses that 80% of the tumors involved both the orbit and the cranial cavity. This fact forms a logical basis for attacking these growths by the intracranial route. The operative procedure, identical with that used for hypophyseal tumors, is well described. The approach visualizes, at the same time, both the cranial and orbital contents and is the only one which allows removal of intracranial extensions and exact identification of the orbital structures.

This presentation of the types, pathology and management of orbital tumors should be of value to both the neurosurgeon and the ophthalmologist. It should make the latter wary of attempting removal, by the anterior or lateral approaches, of tumors lying deep in the orbit, or any in which there is suspicion of intracranial extension.

A. C.

EINFÜHRUNG IN DIE ALLGEMEINE CHIRURGISCHE DIAGNOSTIK. By DR. G. DARDEL, Privat-Dozent für Chirurgie, Bern. Pp. 86. Bern: Hans Huber, 1941. Price, Fr. 6.80.

THIS little paper-bound monograph was written for those young graduates who are beginning their surgical training. It represents the basis of a surgical diagnostic course which the author has given in Bern. He acknowledges the debt he owes to Theodor Kocher and Fritz de Quervain. It includes a great deal of material given in a very abbreviated form. However, it is a good little book and those who can read German fluently will find it useful and helpful.

I. R.

ESSENTIALS OF ENDOCRINOLOGY. By ARTHUR GROLLMAN, PH.D., M.D., Associate Professor of Pharmacology and Experimental Therapeutics in the Medical School of The Johns Hopkins University. Pp. 480; 74 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, \$6.00.

THIS book deals with the fundamentals of endocrinology in a simple, direct manner that should be useful for clinicians and medical students. There are excellent illustrations of gross and microscopic pathology. In spite of this, to the Reviewer, a pathologist, the descriptions in the text of the morphologic changes in disease show a lack of personal experience by the author in the field of pathology. For instance, most pathologists would not agree with the author's explanation of the renal changes in Addison's

disease, his reference to malignant tendencies of adrenal cortical adenomas and some of the descriptions of microscopic lesions in endocrine organs. However, the author, as physiologist and pharmacologist, has an opportunity of treating of those phases more authoritatively than usually can be done in books on endocrinology.

There is an interesting section in each chapter giving a brief historical account of the significant steps in the development of our knowledge of endocrine function and disease. A welcome feature is the absence of enthusiasm for irrational therapeutics so prevalent in many books on endocrinology.

This book will be found a useful source of information for all those who are not primarily endocrinologists.

I. Z.

EXERCISES IN ELECTROCARDIOGRAPHIC INTERPRETATION. By LOUIS N. KATZ, A.B., M.D., Director of Cardiovascular Research, Michael Reese Hospital, Chicago; Assistant Professor of Physiology, University of Chicago. Pp. 222; 128 illustrations, containing 189 electrocardiograms. Philadelphia: Lea & Febiger, 1941. Price, \$5.00.

This atlas is designed to be used in connection with the author's current book entitled "Electrocardiography." It contains examples of the usual tracings to be encountered while reading clinical electrocardiograms, together with adequate explanatory material. A number of tracings labeled "definitely abnormal," might better have been described as "borderline or normal," in the Reviewer's opinion.

W. J.

NEW BOOKS.

Outlines of Industrial Medical Practice. By HOWARD E. COLLIER, M.D. (Edin.), Ch.B., Formerly Reader in Industrial Hygiene and Medicine, University of Birmingham; Certifying Factory Surgeon, etc. Pp. 440. Baltimore: The Williams & Wilkins Company, 1941. Price, \$5.00.

Medical Conferences of the University of Pennsylvania Bicentennial Celebration. *Development of Occlusion (M-12).* By WILLIAM K. GREGORY, B. HOLLY BROADBENT and MILO HELLMAN. (Pp. 72; 49 illustrations. Price, \$1.50.) *The Study of Man (M-B).* By LAWRENCE J. HENDERSON. (Pp. 22. Price, 25c.) Philadelphia: University of Pennsylvania Press, 1941.

Infantile Paralysis. A Symposium delivered at Vanderbilt University, April, 1941. Pp. 239; illustrated. New York: The National Foundation for Infantile Paralysis, Inc., 1941. Price, \$1.25.

Clinical and Experimental Investigations on the Genital Functions and their Hormonal Regulation. By BERNHARD ZONDEK. Pp. 264; 59 illustrations. Baltimore: The Williams & Wilkins Company, 1941. Price, \$4.50.

Papers of Wade Hampton Frost, M.D. A Contribution to Epidemiological Method. Edited by KENNETH F. MAXCY, M.D. Pp. 628; illustrated. New York: The Commonwealth Fund, 1941. Price, \$3.00.

X-Ray Therapy of Chronic Arthritis (Including the X-Ray Diagnosis of the Disease). Preliminary report based on 100 patients treated at Quincy, Illinois. By KARL GOLDHAMER, M.D., Associate Roentgenologist, St. Mary's Hospital and Quincy X-Ray and Radium Laboratories, etc. With a Foreword by HAROLD SWANBERG, B.S., M.D., F.A.C.P., Roentgenologist, St. Mary's and Blessing Hospitals, etc. Pp. 131; 24 original illustrations by author, 2 roentgenograms, and 4 tables. Quincy, Illinois: Radiologic Review Publishing Company, 1941. Price, \$2.00.

Medical Progress Annual 1940. A Series of Fifty-two Reports Published During 1940 in the New England Journal of Medicine. Managing Editor: ROBERT N. NYE, M.D. Pp. 625. Springfield, Ill.: Charles C Thomas, 1941. Price, \$4.00.

Exercises in Electrocardiographic Interpretation. By LOUIS N. KATZ, A.B., M.D., Director of Cardiovascular Research, Michael Reese Hospital, Chicago; Assistant Professor of Physiology, University of Chicago. Pp. 222; 128 engravings containing 189 electrocardiograms. Philadelphia: Lea & Febiger, 1941. Price, \$5.00. (Review, p. 445.)

Electrocardiography. Including an Atlas of Electrocardiograms. By LOUIS N. KATZ, A.B., M.D., Director of Cardiovascular Research, Michael Reese Hospital, Chicago; Assistant Professor of Physiology, University of Chicago. Pp. 580; 402 engravings including 806 electrocardiograms. Philadelphia: Lea & Febiger, 1941. Price, \$10.00.

Doctors Don't Believe It—Why Should You? Facts and Fallacies about Health with Practical Guide for the Layman. By AUGUST A. THOMEN, M.D., with Introductions by LOGAN CLENDENING, M.D., and The Right Honorable LORD HORDER, Physician in Ordinary to the King of England. Pp. 384. New York: Simon and Schuster, 1941. Price, \$2.50.

The Complete Weight Reducer. By C. J. GERLING. Pp. 246. New York: Harvest House, 1941. Price, \$3.00.

The Medical Clinics of North America, Volume 25, No. 4 (Mayo Clinic Number, July 1941). Pp. 302; 88 illustrations. Philadelphia: W. B. Saunders Company, 1941.

The current number of *The Medical Clinics of North America* is devoted to Roentgen rays and radium in diagnosis and treatment. Since the 15 papers are contributed by 10 members of the staff of the Mayo Clinic, there is unusually good correlation of the material.

Lymphatics, Lymph, and Lymphoid Tissue. Their Physiological and Clinical Significance. (Harvard University Monograph in Medicine and Public Health, No. 2.) By CECIL KENT DRINKER, M.D., D.Sc., Professor of Physiology, School of Public Health, Harvard University, and JOSEPH MENDEL YOFFEY, M.Sc., M.D., F.R.C.S. (Eng.), Senior Lecturer in Anatomy, University College of South Wales and Monmouthshire, Cardiff, Wales. Pp. 406; 50 illustrations. Cambridge, Mass.: Harvard University Press, 1941. Price, \$4.00.

NEW EDITIONS.

Applied Pharmacology. By A. J. CLARK, M.C., M.D., F.R.C.P., F.R.S., Professor of Materia Medica and Pharmacology in the University of Edinburgh; Formerly Professor of Pharmacology in the University of Cape Town, and Later in the University of London. Pp. 672; 91 illustrations, and 52 tables. Seventh Edition. Philadelphia: The Blakiston Company, 1940. Price, \$5.50.

Textbook of Bacteriology. By EDWIN O. JORDAN, Ph.D., Late Andrew McLeish Distinguished Service Professor of Bacteriology, University of Chicago, and WILLIAM BURROWS, Ph.D., Assistant Professor of Bacteriology, University of Chicago. Pp. 731; 170 illustrations. Thirteenth Edition, revised. Price, \$6.00.

Essentials of Electrocardiography. For the Student and Practitioner of Medicine. By RICHARD ASHMAN, Ph.D., Professor of Physiology, the Louisiana State University Medical Center; Director of the Heart Station, Charity Hospital of Louisiana, New Orleans, and EDGAR HULL, M.D., Professor of Medicine, Louisiana State University Medical School; Senior Visiting Physician, Charity Hospital of Louisiana, New Orleans. Pp. 373; 122 illustrations. Second Edition. New York: The Macmillan Company, 1941. Price, \$5.00.

PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

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ALLERGY AND RESISTANCE TO INFECTION.

In 1891 Koch described the phenomenon which has since been known by his name. When tuberculous guinea-pigs are reinoculated intracutaneously 4 to 6 weeks after the primary infection there is an intense inflammatory reaction within a few hours, followed by ulceration and ultimately healing without involvement of the regional lymph nodes. Von Pirquet, in 1906, proposed the term "allergy" for this altered response of tuberculous tissue to reinfection. The localizing effect of acute inflammation was already known, and it was natural that the accelerated, intensified inflammation of allergy should be identified with resistance to reinfection (Römer⁴⁶). In more recent years Krause, Zinsser, Opie and many others have more or less completely related immunity in tuberculosis to the allergic state. Zinsser, Ward and Jennings⁵⁹ concluded in 1925 "the artificial production of allergy by dead bacilli or other products appears a hopeful direction for the investigation of immunization in tuberculosis." The concept was extended to infection in general. Probably the most widely quoted opinion in contemporary discussion is due to Opie,^{36b} "Both with anaphylactic inflammation and with the inflammatory reaction of infected animals, vital organs are protected at the expense of local injury."

During the last decade the dissenting voices of Rich and his associates have been largely responsible for the increasing doubts cast on the allergic reaction as a mechanism whereby invading bacteria are localized or destroyed. It is to be suspected that their cogent arguments have modified some of the opposing views. In 1936, for example, Opie^{36c} wrote: "In the process of local fixation it is not possible to estimate the relative importance of antibodies, of phagocytes and of the inflammatory reaction itself." Rich feels that the factors which govern resistance to infection are quite separate and distinct from those concerned in allergic inflammation even though both attributes result from

the same exposure. This does not imply that hypersensitivity does not modify the operation of immunity. Indeed Rich and McCordock,⁴³ in 1929, pointed out that increased transudation from the blood-vessels must, by dilution, help to neutralize the injurious effects of the products of bacterial disintegration in the hypersensitive body. The same process clearly makes available to the tissues whatever factors of protection circulate in the blood. Conversely, those very products of bacterial disintegration, in comparable concentration, would not cause necrosis of normal non-sensitized tissue.

Many of the earlier writings concerning the relation between allergy and immunity dealt with the events which follow parenteral introduction into an animal of heterologous protein. The identity of the "immune body" responsible for anaphylactic sensitization and for the various *in vitro* "immunity" tests was established, and it became a commonplace not only to state that hypersensitivity is a stage in the development of immunity, but to transfer the reasoning from inert molecular protein to bacterial allergy, and resistance to living self-propagating infective agents. The correlation may exist in respect of these bacterial components which behave after the fashion of heterologous proteins, that is, yield humoral antibodies, passively sensitize the guinea-pig uterus, and exhibit an immediate hypersensitive response.

The Nature of the Hypersensitive State. Microorganisms are complex chemical entities. During infection the tissues may become sensitized both to polysaccharide and protein. There is overwhelming evidence that the delayed tuberculin type of hypersensitivity due to the protein of microorganisms is unaccompanied by humoral antibody, and cannot be passively transferred to normal animals. It is achieved only by the introduction of intact bacteria, alive or dead. Hypersensitivity produced by the injection of bacterial proteins conforms to the anaphylactic type, and while the tissues react violently and immediately to that protein, they will not react hypersensitively to the injection of the intact bacteria (Baldwin;² Bouquet, Sandor and Schaefer;⁵ Rich;^{40b} Sabin and Joyner⁴⁹). As Rich^{40c} pointed out in 1941, this type of experiment has no relation to bacterial allergy, in which condition an antibody mechanism is predicated only on the specificity of the reaction and the fact of desensitization.

The hypersensitivity is a property of the individual cell. Holst²³ and Stewart and coworkers⁵² showed that the addition of tuberculin to leukocytes from animals hypersensitive to it kills the cells. Rich and Lewis,⁴² using the tissue culture technique, showed that cells from the blood and fixed tissues of tubercular animals were distinctly more susceptible to the toxic action of tuberculin than were normal cells. Aronson^{1a} and Moen and Swift³⁴ confirmed these findings and found that the sensitivity persisted through several transplants. They suggested, therefore, that this "represented a more or less permanent acquired characteristic impressed on the cell as a result of the infection." Moen³³ later showed a similar effect in cultures of mononuclear cells obtained from the pleural cavities of tuberculous animals and found the tuberculin sensitivity to extend through three transplants over a period of 29 days. This raises the question of how valuable is the increased phagocytic capacity of mononuclears derived from actively

tuberculous or vaccinated guinea-pigs for tubercle bacilli, as Lurie^{27b} found. This cellular hypersensitivity must mitigate against survival of the phagocytic cells. That phagocytosis may aid in the dissemination of microorganisms was beautifully reemphasized by Goodpasture and Anderson²⁰ in the living tissues of the chick embryo.

By contrast, the allergy which develops to bacterial polysaccharide is of the immediate anaphylactic type, and usually is accompanied by circulating antibody (Harley²¹). The correlation between allergy and antibody is less exact in normal persons (Tillett and Francis,⁵⁴ Finland and Sutliff¹⁵) due possibly to difficulties in titrating small amounts of the antibody and to the well-known inverse relationship between anaphylactic sensitivity of the individual cells in tissue culture are not affected by the addition of the specific antigen (Aronson¹⁶). This is in agreement with the views of Opie that local anaphylaxis depends on a precipitin reaction and serves to fix the antigen within the tissue spaces. That type-specific antibody, without the intervention of inflammation, likewise fixes the pneumococcus, was shown by Rich and McKee.⁴⁴ Nevertheless, the rapid inflammatory response may serve to support the mechanism of resistance, even though it is not the prime factor, by facilitating access to the tissue spaces of antibody and phagocyte. Freund¹⁷ and Douglas and Simpson¹² concluded that antibody permeates the fluids of the uninflamed tissues everywhere. McMaster and Parsons,³⁰ on the other hand, do not believe extracellular fluid exists in mammals under normal circumstances, but Maurer³¹ succeeded in collecting from the extracellular spaces of frog muscle a clear fluid which had a protein content of 1.53% as compared with a serum protein of 4.23% from the same animals. Frogs and mammals differ markedly in the permeability of vessel walls, and it may be recalled that Krogh, Landis and Turner²⁵ considered the filtrate from human capillaries to contain less than 0.1% of protein. Thoracic duct lymph is this filtrate usually concentrated by absorption of water and salts. At any rate, the possibility exists that antibody globulin may be present in the blood and tissue spaces in markedly different concentration. The increased capillary permeability which follows even trivial damage to the tissue (Rous and Smith⁴⁸) must tend towards equalization of the two concentrations. Indeed, Lurie^{27b} found that typhoid agglutinins collected in the pleural cavity of tuberculous guinea-pigs as a result of a chemically induced inflammation to a concentration higher than that in the blood. Mention must be made, too, of the work of Dienes¹⁰ who considers that the early stages of specific immunity are associated with absence of circulating antibody and a delayed tuberculin type of reactivity. McBroom and Schlesinger²⁸ obtained similar evidence. It is difficult to say how far this reconciles the differences between protein and polysaccharide sensitivities.

The tissue response in allergic inflammation does not differ qualitatively from that due to acute inflammation produced by any irritant in the normal body. The vascular and cellular changes are identical. Dienes and Mallory¹¹ considered that in hypersensitive inflammation mononuclear cells predominate in the exudate from the beginning. Most observers, however, agree that the normal sequence of polynuclear,

mononuclear cells is followed. The actual physiologic stimulus which determines these changes is the liberation of histamine and the substance discovered and named leukotaxine by Menkin.

Finally, as far as generalizations can be drawn from infections of different types, the problem under discussion is this. The immune animal potentially possesses phagocytic and antibody mechanisms of resistance, and two conditions of hypersensitivity by which specific inflammation can be provoked. Are these latter essential or beneficial to the animal in its efforts to combat infection?

Does Allergic Inflammation Localize Infection? The path of absorption of chemical substances from the tissues depends on the size of their molecules; the smaller molecules are absorbed by the blood stream, the larger by the lymphatics (Drinker and Field¹⁵). It was shown many years ago (Noetzel¹⁶) that bacteria travel from the tissues by the lymphatics rather than the blood stream. Barnes and Trueta³ showed that bacteria placed in freshly made wounds could be found only in the lymphatics. This agrees with the observation of McMaster and Hudack,²⁹ that in freshly made wounds the blood-vessels shut down and thrombose within a few minutes of the injury, while the lymph-vessels remained patent for over 48 hours.

Since the observations of Issaef in 1894 it has never been questioned that well-established inflammation forms a mechanical barrier which limits the dissemination of bacteria and other particulate matter, with a few exceptions, depending on the variety and virulence of the organism (Cannon and Hartley;⁷ Clark⁵). The effect was ascribed to a wall of macrophages by Gay and Morrison,¹⁹ to neutrophils by Clark.⁵ Opie²⁸ showed that in local anaphylactic inflammation the small blood-vessels and lymphatics are injured and often undergo thrombosis. Menkin in an extended series of papers has emphasized the importance of this lymphatic blockage in localizing infection.

When bacteria, however, are introduced into the normal tissues of an animal, dissemination may take place before sealing of the lymphatics or mobilization of leukocytes can occur. Rivers and Tillett⁴⁵ found that a mild inflammatory irritant such as beef broth injected into the skin of rabbits protected against streptococci injected 24 hours later, but did not protect when organism and irritant were injected together. This was confirmed by Rich⁴⁶ and Menkin himself²² found that for the localization of ferric chloride or colloidal iron in a chemically inflamed area the irritant must be injected some time previously. In some cases the spread of bacteria was hastened.

The immediate fate of microorganisms which gain access to the tissues is determined by the dynamics of capillary and lymphatic function in the early stages of inflammation. As far as the vascular bed is concerned, the main changes are vasodilatation with an increase in capillary pressure and permeability. These are responsible for the increased capillary filtration, and for the parallel increase in lymph flow and pressure (Field, Drinker and White;¹⁴ Barnes and Trueta³). There seems no reason to doubt that edema and increased lymph flow *per se* facilitate dissemination (Rhoads and Goodner,²³ Rich and McKee,⁴⁴ Lurie^{27a}). After an interval of time, and one school of thought (as logic demands) has endeavored to show how short this important interval may be,

the lymphatics become occluded by fibrin thrombi. Menkin considers that retention of materials in an acutely inflamed area depends on the fibrin network formed in the edematous tissue spaces or in lymphatic vessels. He showed, moreover, that the rapidity with which bacteria are walled off by this process is a function of the intensity of the injury they cause, and this in turn varies with the nature of the microörganism. For example, *Staph. aureus* introduced locally induces lymphatic blockage within an hour, whereas after cutaneous inoculation of hemolytic streptococci the lymph channels are open as long as 2 days. These events appear to be related, not to the plasma coagulase effect of the one and the fibrinolytic effect of the other, but to the degree of tissue damage. It is perhaps significant that Lurie^{27a} found on introducing melted agar impregnated with tubercle bacilli and trypan blue subcutaneously into normal and highly immunized rabbits, the early rush of lymph from the focus of reinfection was so intense that both bacilli and dye were swept over to the draining lymph nodes much more rapidly in the sensitized than in the normal animal. He stated,^{27b} "However, one cannot conclude from this that in man also the exaggerated inflammation aids rather than hinders the dissemination of the bacilli of reinfection. Rabbits become only moderately sensitized to the tubercle bacillus, as compared to the exquisite sensitivity that man acquires as a result of a tuberculous infection." Lurie therefore repeated the experiment on guinea-pigs and found that the bacilli of reinfection are more effectively fixed at the portal of entry in a sensitized and immunized pig than in a comparable rabbit. This he correlated with the greater degree of injury in the guinea-pig, the more abundant exudate and a histologic demonstration of the more rapid thrombosis of the adjoining lymph-vessels to give a clot with a finer sieve formation than does the rabbit. The correlation was clouded somewhat by finding that the human gave a clot histologically of the rabbit type. Thus, Menkin and Lurie demand an intense degree of inflammation for localization, and admit that minor degrees may aid dissemination. This contrasts with the views of other protagonists of the allergic theory. Wilson *et al.*,⁵⁸ for example, find that a mild degree of inflammation assisted their guinea-pigs to resist tuberculous reinfection: a high degree "was worse than no allergy at all."

What bearing does this have on the inflammation of allergy? Rich pointed out in 1930 that the deposition of bacteria in an area that is *already inflamed* when the bacteria are introduced is not comparable with what occurs in a hypersensitive reaction, when the inflammatory reaction must develop after they reach the tissues. Bacteria have long been known to spread with great rapidity from the portal of entry in the normal animal. Noetzel, for example, in 1906 found bacteria in the regional lymph glands 5 to 10 minutes after they were injected into the knee joints of rabbits. Rich and McKee stated in 1934 that "since the time required for an effective amount of inflammation to appear about invasive bacteria, even in the allergic body in which the process is accelerated, has been found by all who have investigated the matter to be distinctly longer than the time required for bacteria to spread from the site at which they lodge." Rich had shown experimentally in 1930 that the injection of a mixture of two bacteria into

an animal hypersensitive to one of them, even though it reproduced the time conditions of an accelerated hypersensitive inflammation in the previously normal tissues, the spread of the bacteria to which the animal was not immune was accelerated rather than retarded. Cannon and Hartley⁷ and others confirmed this failure of allergic inflammation to protect rabbits against pneumococcal infection. Rich and McKee⁴⁴ concluded that the primary localization is accomplished by the immune antibody, which acts to hold the bacteria at the site until the leukocytes can emigrate to attack and destroy them. After producing with benzol a leukopenia in immunized rabbits, they found that virulent Type I pneumococci, introduced intracutaneously, proliferate, but adhere to each other and to the tissues as well for hours after the controls have died with septicemia, even in the absence of microscopically detectable inflammatory exudate or thrombosis of lymphatics. In the absence of the leukocytes growth of the pneumococci proceeded to form large agglutinated masses in the tissues, until they penetrated the blood stream and the animal died with septicemia, even though its plasma was capable of passively protecting non-immune animals possessing leukocytes.

It has already been pointed out that allergic inflammation may be associated with a faster or slower rate of spread of tubercle bacilli than in normal controls.

Does Allergic Inflammation Prevent Proliferation? Many of the recorded observations either indicate that inflammation is not required, or fail to distinguish events occurring in an allergic animal from events due to the allergic state.

The numerous papers of Rich and his associates testify that in pneumococcus immunity localization and destruction of the bacteria are carried out by antibodies and phagocytes. The work has been amply confirmed (Rich^{40c}). That hypersensitivity adds nothing to this effective immunity is indicated by Rich and Brown.⁴¹ They showed that if the serum of animals that are hypersensitive and immune to the pneumococcus is injected intravenously into normal animals, the immunity is transferred but not the sensitivity.

Lurie^{27b} reported quantitative determinations of surviving and metastasizing tubercle bacilli introduced into normal and sensitized (B.C.G.) guinea-pigs and rabbits. He found marked inhibition in the multiplication of the organisms in the cell-free body fluids, and noted without comment the numerous unsuccessful attempts to demonstrate *in vitro* bactericidal properties of serum derived from animals immunized against tuberculosis. Freund and Angevine¹⁸ in rabbits pretreated with heat-killed tubercle bacilli intracutaneously concluded that virulent tubercle bacilli introduced by the same route multiply actively at the site of injection during the period of retarded lymphatic dissemination, and that the retardation is caused by local fixation and not by destruction of the organisms. The conclusion was correct in the sense that ample numbers of bacteria were present locally for spread to occur if the channels were open, but their figures show pretty well as much interference with local multiplication as with dissemination in the immunized animals. It will be recalled that Lurie^{27a} found sensitization of the rabbit to promote lymphatic spread.

Immunity and Allergy as Independent Variables. The spontaneous waning of tuberculin sensitivity with persistence of acquired immunity suggests their independence. Willis⁵⁶ disagreed with this view in contending that reinfection caused hypersensitivity (and therefore resistance) to reappear in a shorter time than in non-immune controls. Selwabacher and Wilson,⁵⁰ and Wells and Brooke⁵⁵ found, on the contrary, that the development of hypersensitivity was delayed following reinfection. Freund and Angevine¹⁸ raised a further criticism, which might be levelled at many other studies, of Birkhaug's⁴ conclusion, that desensitization assists the resistance to reinfection, because Birkhaug did not show his animals to be desensitized both to tuberculin and living tubercle bacilli.

A varying ratio of the two components, hypersensitivity and resistance, to infection has been shown to depend on the route of immunization. Petroff, Branch and Jennings,³⁷ and Branch and Cuff⁶ found that intravenous immunization with killed tubercle bacilli rarely induced tuberculin sensitiveness, whereas subcutaneous inoculation, for instance, established the same degree of immunity as well as hypersensitivity. Swift and Derick⁵³ similarly dissociated allergy and resistance, using streptococci. Many workers have stressed the efficacy of intracutaneous inoculation in inducing hypersensitiveness (Julianelle,²⁴ McBroom and Schlesinger²⁸). Dienes and Schlesinger and McBroom, however, return to an earlier viewpoint and believe that allergy so induced is not only in part responsible for the early stages of the immune state, but that the early phase represents a tissue immunity in which fully developed resistance is associated with humoral antibody. It is difficult to fit this concept in with the experimental characteristics of the tuberculin type of sensitivity.

There is no need to review again the impressive testimony that desensitization experimentally, and maybe clinically, can abolish hypersensitivity and leave resistance intact. Rich^{40c} gives an excellent bibliography. Those who feel that allergy is unrelated to immunity accept these experiments at face value: their critics find plenty to criticize. Freund and Angevine¹⁸ would not accept tuberculin desensitization as proof of desensitization to intact bacteria. They feel that the large number of deaths in prolonged desensitization of vaccinated animals invalidated the experiments of Rothschild *et al.*⁴⁷ It seems natural that continued administration of large amounts of tuberculin over a period of months should impair the health of well or sick animals. In this respect Willis and Woodruff⁵⁷ suggested that the inanition, emaciation, and ulcers of the skin which followed daily injections of large doses of tuberculin may all be factors in bringing about the difference between the amount of tuberculosis in the desensitized and untreated animals. In a surprising pair of papers Wilson and his associates⁵⁸ state at the outset a disagreement with Rich's view that allergy plays no part in immunity. Their experiments on desensitization support Rich in entirety, the desensitized animals survived longer and had fewer lesions postmortem than allergic non-desensitized animals. Their discussion is a reconciliation of experiment and conclusion. They found a relation between the degree of sensitivity to tuberculin at the time of reinfection and survival time, and suggested that "(1) a slight

to moderate degree of allergy at the time of infection is favourable to survival, (2) a high degree of allergy is definitely unfavourable, (3) a very high degree of allergy is worse than no allergy at all." With less conviction and somewhat paradoxically they concluded that the higher the degree of sensitivity to tuberculin reached *after* injection, the longer the survival time. How this affects the fate of surviving bacteria is not clarified. Anent the question of desensitizing doses of tuberculin, they raise again the question of their immunizing value, in spite of numerous studies to the contrary, and despite the fact that, as Rich points out, it is the question of the hypersensitive state which is at stake. Tangentially, they then question whether desensitization is complete anyway, and suggest that repeated injection may maintain minor inflammatory reactions around each tuberculous focus in the body, with the result that the dissemination of the bacilli is retarded, and the rapid caseation which seems more liable to occur in the highly allergic animal is prevented.

The Effect on the Lesions. In tuberculosis, tubercle formation is incited by the lipoid fraction of the bacillus. Through the tissue culture studies mentioned above it has become clear that necrosis in these tubercles is the result of contact of hypersensitive cells with tuberculo-protein. The vascular changes accompanying inflammation are not essential to the process of caseation. Quantitatively it is likely that the amount of tuberculo-protein necessary will vary with the degree of hypersensitivity of the individual cells, and in general will require some multiplication of the bacteria if the numbers which gain access to a given site is small. A given number of bacteria will do less damage in a normal than in a hypersensitive body, and their effect can be minimized by desensitization (Rothschild;⁴⁷ Wilson⁵⁸). Wilson and coworkers believe desensitized animals live longer than controls and show less severe lesions because in the controls "allergy has been allowed to develop to a point at which the very intensity of the reaction in the internal organs—particularly the lungs—proves prejudicial to life." Freund and Angevine¹⁸ believe that the allergic reaction in the skin of intracutaneously inoculated animals protects the rest of the body. They state, however, "it is conceivable that allergic reaction in internal organs also promotes the formation of tubercles and development of caseous necrosis." Manifestly all shades of opinion dislike marked allergic inflammation in the viscera. Henrici²² correctly emphasized the importance of considering the site of the allergic reaction. In the Koch phenomenon the organisms and the products of the reaction are cast off to the exterior; when the same reaction occurs in the lung or kidney it may result in an extension of the disease.

Coccidioidal granuloma is the reinfection form of San Joaquin "valley fever" or "desert fever," appearing after the skin tests are positive. The mortality in primary infection is virtually *nil*, in the reinfection type about 50% (Dickson and Gifford⁹). However, only 1 in 354 cases of "valley fever" goes on to granuloma. Henrici suggests that in all the deep-seated mycoses the progressive course and lesions are dependent on the state of hypersensitiveness which develops in the patient. He points out, too, that in the dermatomycoses the ultimate healing of the lesion is due to the allergic state.

Opportunity for exposure and sensitization increases with age, and reasonably contributes to the age differences in both the acute and chronic disease, particularly if the portal of entry is the respiratory tract. Lauehc²⁶ pointed out that lobar pneumonia, which is rare in young infants, may occur in the first few days of life, and increasingly frequently as infancy is passed. Lauehc regards lobar pneumonia as the response of an allergic body having a partial immunity to the infecting type of organism, the sensitization of the infants being passively transferred *in utero*, the adult being sensitized as a result of minor upper respiratory infections. According to this view, allergy to the pneumococcus does play a part in the development of lobar pneumonia. Sharp and Blake⁵¹ and others provided experimental support for this contention. Reimann³⁸ suggests that the tendency for recurrence of lobar pneumonia in the same individual is due to persistence of this allergic state. Recurrences have the same type distribution as first infections (Finland and Winkler¹⁶) but the incidence of bacteremia and the case fatality rate seems generally lower. One explanation of this paradox of increased susceptibility and greater resistance is that the one depends on nucleoprotein sensitization and the other on antipolysaccharide antibody. Opie^{36c} considered that while allergy was not essential in the production of diseases like lobar pneumonia, rheumatic fever, glomerulonephritis, it may modify their course.

Conclusion. The burden of proof appears to be with those who believe that hypersensitive inflammation is an important mechanism in resistance to infection. Moreover, in chronic disease like tuberculosis, the tissue destruction is a manifestation of allergy. This is not to deny the value of vaccines or first infection as an immunizing experience, nor is it necessary to debate the merits of these procedures.

The mechanisms of resistance differ widely in respect of different infective agents, and in some diseases like tuberculosis there exists no clear basis for the state of resistance. It would seem logical to conclude that allergic phenomena would differ vastly, therefore, in importance, in diseases like diphtheria, pneumococcal infection and tuberculosis.

In Gay's textbook of 1935, *Agents of Disease and Host Resistance*, the Scegals divided infections into three categories: those in which allergy played no part in resistance, those in which allergy assists resistance and those in which it handicaps resistance. This opinion, to which Rich subscribes, is probably nearer the truth than the extremists of either school in the controversy.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY.

UNDER THE CHARGE OF

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CONSTITUTIONAL TYPES AND SUSCEPTIBILITY TO PARALYSIS IN POLIOMYELITIS.

EVEN in the earliest writings about poliomyelitis, there is found the suggestion that the paralytic disease exhibits a tendency to selective occurrence in certain types of individuals. The first account of what is clearly poliomyelitis is believed to be Underwood's description in

1799;²⁷ in which he remarks, "I have seen it in others who are older, and the finest children." Similar notations are found in the observations of other clinicians during the 19th century. Shaw (1823), "... strong and healthy children are more frequently affected than those of a weakly constitution." Heine (1840), "Before the illness there had been complete health and well-being, and a strong and blooming bodily constitution." Sinkler (1875),²³ "The affection usually occurs in a strong, healthy child between 6 months and $2\frac{1}{2}$ years of age. . . . J. R. L., age 4 years, was brought to my clinic November 18, 1874. . . . Is a robust, healthy looking boy, with light hair, blue eyes and sound teeth. . . . The excellent state of the general health in this affection is very striking. . . . Almost all of the children who are brought to our clinic suffering from infantile palsy are remarkable for their fine, healthy appearance." Caverly (1896):⁸ "Case 1. Boy 3 years; previous health good; active child; stronger than his brother 2 years older. Case 2. Boy, $3\frac{1}{2}$ years; sturdy child; most active of a family of 3 children. . . . Of the 46 cases in which the previous health of the sufferer is given, in 35 it is good and in 11 it is poor. It is quite certain that the strong, healthy children preponderated." Madison Taylor (1898):¹⁹ "A. C., age 12, was a perfectly vigorous boy until a fortnight previous. . . . D. B., age 4, a fine vigorous boy, the first child of young, handsome parents. . . . R. P., a robust boy 2 years and 5 months. . . . G. S., a healthy girl of 10 years and 6 months." Hill (1909):¹⁶ "As a general rule, the children affected had been exceptionally robust and active, with good appetites and living on a general diet." Wickman (1913):²⁸ "Heine-Medin's disease usually attacks those in perfect health."

Such exclamatory comments concerning children attacked by paralytic poliomyelitis, appearing in studies of the disease before the virus and its mode of spread became the center of attention, are enough to indicate that whatever individual predisposition there may be, it does not reside in being "run-down" in the ordinary sense of the word. There is tacit agreement today among many clinicians with the ideas expressed by these earlier students as shown, for example, by their frequent reaction to the epidemiologic evidence that individual susceptibility to paralysis is a major determinant. Many physicians, and even laymen, when it is suggested that among the many exposed to the virus only the few susceptibles are paralyzed, insist that they are not "run-down;" the general assumption being that susceptibility to infection is the result of a "run-down" condition in the ordinary sense—undersize, underweight, undernourished, and the like. Thelander and Pryor²⁶ have stated, "Our observations bear out those of others that it is not the delicate, handicapped child that is most frequently the victim of poliomyelitis, but just as often the most sturdy. That some of our choicest and handsomest children are endocrine anomalies, . . . however, is not borne out by our studies" (anthropometric).

But in earlier times, these ideas did not take root as a fundamental epidemiologic feature of the disease. The demonstration of its infectious nature, the isolation of the virus, and the experimental transmission of the disease had, by 1916, shifted emphasis to the mode of spread as the important epidemiologic determinant. Although much evidence had accumulated that dissemination of the virus is widespread and

that abortive cases or healthy carriers play the major rôle (Wickman, Caverly, Flexner and his co-workers), paralysis occurring only in the minority of those exposed, the reasons were sought in parasitic and environmental rather than host factors.

In the flush of this period of bacteriologic observations, during the 1916 epidemic, Draper^{9a} broke away from conventional trends with the following clinical observation.

"The patients displayed certain definite morphologic characteristics which appeared with insistent regularity. The type of child which seems most susceptible to the disease is the large, well-grown, plump individual who has certain definite characteristics of face and jaws; is broad browed and broad and round of face. The teeth are particularly interesting. It was noted that in 50 to 60 per cent of all the cases in the hospital at Locust Valley, the central incisor teeth of the upper jaw were separated by a cleft of varying width. The wide-spaced dentition has been a striking feature and frequently involves all the single teeth of both jaws, so that each tooth stands entirely free."

"Among the adolescents and young adults who acquired poliomyelitis and in whom the disease seemed always to be most severe and, indeed, usually fatal, the type differed from that just described. Instead of the very large, well-nourished individuals with widely spaced teeth, there appeared a more delicately made type. Of the 6 or 8 fatal cases in young adults, seen by the writer, the similarity of appearance of the individuals was so striking that all might have been of one family. All were brunettes, with very delicate dark skins and high coloring of cheeks and lips. Often small, deeply pigmented moles were present on face or neck. There was in every case a definite though finely chiseled maxillary prognathism, and instead of dental separations a tendency to crowding of the teeth. This type was so definitely associated with the severe form of the disease that we have come to attach grave prognostic significance to it. In this connection, it is interesting to note that a surprising number of the fathers of children ill with poliomyelitis presented striking anthropologic markings. Thus one was a definite acromegalic, while two others were clearly Froehlich types, dark-haired, fat faces and bodies, narrow shoulders, broad hips and knock-knees. In three others, maxillary prognathism was marked, and although the body stature was small the hands were very large and broad, and there was great physical strength. A seventh father had widely separated upper incisor teeth and was a tall, big-boned individual. Four of the mothers in this group had moderate or marked exophthalmos and were high strung, intensely nervous women. In another instance, the mother of two desperately ill cases had an unusual degree of maxillary prognathism."

"Whether or not these facts have a bearing on the question of susceptibility is still problematical. The cited examples, however, are merely a few of the very many similar observations made throughout the summer by the diagnosticians of the New York State Department of Health on Long Island. It is interesting, too, to record the numerous instances of 2, 3, 4 and 5 cases in families with such parental types, suggesting possibly a true family susceptibility."

In a later paper, Draper^{9b} stated: "The foregoing observations

gave impulse to investigate the general topic of human constitution in relation to disease. The point of view in regard to this matter and the technical methods which have been developed during the intervening years have been applied to cases arising in the epidemic which has just drawn to a close (1931)."

"Some of the morphologic characters of this group of people which differ from the general population can be demonstrated by anthropometry and expressed in numerical values. Other features cannot be subjected to mensuration. But observational and descriptive methods suffice to display the striking qualities. The interpupillary space is unusually wide. This feature is not only emphasized in relation with the upper face (nasion-prosthion) but likewise with the facial diameter, although the latter is also unusually wide. These characteristics, in addition to the somewhat greater distance between the inner canthi, give to the face of these children the broad, wide-eyed expression which was previously noted. In almost all cases there is a definite overbite and frequently a noticeable or pronounced maxillary prognathism. The gonial angle formed by the ascending and horizontal rami is more obtuse in the subject of infantile paralysis than in the members of the control series of miscellaneous diseases. This character is similar to that found in adults of the so-called asthenic variety, as for example, members of the peptic ulcer group who display a rapidly exhaustible energy capacity (adrenal). The narrow subcostal angle is likewise characteristic of these. In this series the inner border of the scapula was not more frequently concave than in the controls. It is interesting to note that, in paradoxical association with these evidences of the gracile form, the subjects of acute anterior poliomyelitis tend to gain weight and are often definitely pudgy, fat types. The hand index (breadth-length ratio) shows a short, broad form. This is ordinarily correlated with acromegaloid trends in the facial structure. So far as the rest of the body is concerned, the one outstanding measurable character is the biiliac-biacromial diameter ratio. The pelvis of these individuals is definitely wide as compared with the shoulders. This character is generally accepted as a definite mark of the neuter or feminine type. In both sexes it marks that deficient gonad activity which results in retarded development, and checks metamorphosis toward the finished form of the mature individual of either sex. While this characteristic is usually associated with curving body contour and feminine fat deposits, there are certain individuals afflicted with infantile paralysis who differ. These, on the contrary, are long, lanky, and often possess exceedingly large long-boned hands. Certain of the young male adults are of this type. As might be expected in the individuals with feminine contours and increased fat, the external genitalia are small; the penis less than average size with pointed glans. The scrotal sac is short. Several cases of unilateral cryptorchidism appeared, and numerous instances of short spermatic chord which resulted in a partial cryptorchidism on contraction of the cremaster muscles. Before puberty the rotund contours of the male children resemble those of females. But there are no especially striking physical proportion aspects of the adolescent girls or adult women. Comparatively few of these, however, are stricken."

It is evident that Draper encompassed more than dimensions in his concept of the type of individual which he regarded as susceptible to paralysis. Thus, he writes:^{9c}

"If perhaps *homo sapiens* had spent a fraction of the energy in the effort to explain himself as he has poured through his intellect upon the rocks, the trees and other animals, he would doubtless be wiser even than he is today. But it is only within the last quarter-century that he began rationally to face the humiliating realization that an adverse environment is not the sole cause of such troubles as may befall him."

"Medicine focussed on sick spots in organisms which were partially or totally out of commission. Somewhere back in 1912 or so, Dr. Jelliffe passed the notion on to me in one of his flaming utterances. And, subsequently, it has always been an honest gratification to me when, on occasion, I've handed the ideas back to him dressed in anthropometric clothing or gossamer philosophic veils and he has accepted them for publication in his journal."

"I have often wondered why it was that the psychiatric branch of medicine was more receptive to and sought more eagerly than the others to understand the creature man; why the psychiatrists before the others strove to capture that quality which Samuel Butler called 'personal identity' and D. H. Lawrence simply 'otherness.' Perhaps the fascination of watching the wheels go around in reality, the respiratory rhythm, the passage of a nerve impulse, the amazing and subtle electro-potential flowing from cardiac systole, explains our delinquency. Perhaps the mechanisms trapped the internist's imagination and surely any one of them would suffice. . . . But, you cannot study the heart's function by itself and hope to comprehend the creature man. Furthermore, the internist has been forced to give immediate relief for suffering. He inevitably must focus upon an ailing area or organ. The psychiatrist, on the other hand, from the time of his internship has ever faced the whole person in action: how does he look? what does he do? what sort of creature can he be? Such questions by virtue of their social implications encourage the notion of personal identity or otherness."

"For the internist to be powerfully impressed by this last named quality of a human being, a large epidemic is almost essential. The clinical observer of such a calamity cannot fail to perceive that stricken persons are of quite a different stripe from those who remain well"—simply another way of saying that stronger impressions come from seeing large numbers of cases within a sufficiently short space of time to enable one to visualize them as a group.

Draper and Dupertuis¹⁰ continued studies of the evaluation of constitutional characters of paralyzed persons over a period of years. The method used for studying the external morphology was composed of mensuration, observation and statistical analysis. The findings indicate that persons susceptible to the virus of acute poliomyelitis possess a special constitutional type of morphology which differs significantly from that of non-susceptibles. Variations occur in the degree of morphological differences, extending from those imperceptible to those of high statistical significance. Among susceptibles, there is a lack of coördination between growth and development which is expressed in a tendency to overgrowth and retarded development.

The peculiar presence of the Mongoloid eye and the fetal and infant-like retardation of the eye-nose zone suggest adverse genetic or intra-uterine forces. The person susceptible to infantile paralysis is a different and in some way incomplete phenotype.

These morphological observations were analyzed by statistical methods and the original findings largely substantiated. According to the indices used by these investigators, paralyzed individuals showed a higher percentage of a greater number of the pertinent characters than the normal. They point out, however, that human morphology is significant only insofar as it correlates with other characters of the total personality.

Dissenting views of Draper's thesis have been taken by Levine, Neal and Park,¹⁸ and also by Thelander and Pryor.²⁶ The former investigators used relatively few measurements, no one of which showed a difference; and the average age of their patients was 4.5 years, whereas in the studies reported by Draper the mean age was 9 years. Thelander and Pryor, using a number of anthropometric indices, could find no demonstrable differences in anatomical characteristics between 100 children paralyzed from poliomyelitis and 518 normal controls of the same age and sex. It is not clear from their paper that some of the measurements were not influenced by effects of the disease. For example, patients with atrophy of one or both shoulders were apparently included in their series of biacromial diameter observations.

Draper has always taken into account the whole individual, stating, "Afflicted children have something about their appearance and form and expression definitely absent in those who escape. . . . It would seem that the paralyzed child possesses the same essential otherness in susceptibility as does the necessary virus,"^{26c} while in the two studies cited which differ from his thesis, the observations have been confined to measurable dimensions, no one of which considered separately would necessarily be a measure of susceptibility. Thelander and Pryor have said, either facetiously or naively, "That variations in susceptibility exist cannot be denied, but that these variations in susceptibility to an ultramicroscopic organism can be measured by centimeters and grams in a highly complex physicochemical and electrodynamic nature, such as the human body with heredity linked to chromosomes, genes and protons, does not necessarily follow."

Epidemiologically, there are indications which point to differences in the exposed, rather than differences in exposure, as determining the occurrence of paralytic poliomyelitis. Expressions of the widespread and more or less uniform dissemination of the virus are seen in such features of the clinical disease as age distribution^{3a} and geographic prevalence,^{3b} in the gradation from frank to mild or suspected abortive forms of the disease, and in the development of serologic immunity in those who do not have the disease in recognizable form.⁵ The limited and selective occurrence of the frank disease, however, is apparent in the tendency to familial occurrence,⁴ in seasonal and climatic variations in the frequency with which exposure to the virus results in the paralytic disease,^{3b} in its occurrence following operations on the upper respiratory mucous membrane^{6,7,11,25} and in its association with pregnancy.^{3c,e}

That poliomyelitis occurs excessively often during the latter months

of pregnancy is a clinical impression which is in conformity with the view that endocrine differences are involved in susceptibility to the virus. Among the changes which accompany pregnancy are those of mucous membrane, which are attributed to alterations in the economy of estrogenic substance.

The weight of evidence in poliomyelitis implicates the nasal mucosa as a portal of entry of the virus. That a disturbance of this structure may open up the pathway for the entrance of the infectious agent is strikingly shown in the occurrence of bulbar poliomyelitis following tonsillectomy and adenoidectomy. Thus, the suspected selectivity seen in the occurrence of paralytic poliomyelitis in the latter half of pregnancy suggests the involvement of estrogenic substance in susceptibility, and gives some indication as to the possible manner of its operation: through mucous membrane alterations.

While no weight can be given to single instances, there are two occurrences of poliomyelitis recorded in endocrinopathic individuals which, because of the uncommonness of the disease and the even greater rarity of the endocrinopathies in the general population, are impressive when taken together. In four types of "juvenile adiposogenital hypopituitarism" cited in a study,¹² one had suffered an attack of poliomyelitis. The other instance is an attack of poliomyelitis in an adult male castrate individual seen by the author.

Experimentally, it has been shown that castration of immature female monkeys (*Macacus rhesus*) results in thinning of the genital mucosa, and that the administration of estrogens to such animals effects a recornification of the genital mucosa.¹ The nasal mucosa participates in these changes.²²

Experiments have been reported by the author^{3c} in which castrate immature female monkeys developed poliomyelitis following intranasal instillation of virus more promptly and with greater frequency than castrate immature female monkeys prepared by preliminary injections of estrin (Amniotin Squibb), and the reaction maintained through the period of virus instillations. Exact comparison could not be made between these results and our general experience with intranasal instillation of virus because of difference in experimental set-up, but there was a pronounced dissimilarity between the results in castrate monkeys and estrin-treated castrate monkeys. Whether the castrate animals were more susceptible than normal animals, or the estrin-treated animals more resistant was not clear. However, our interpretation in view of general experience with intranasal instillations of virus, and perhaps influenced to an extent by theoretical reasons for believing that castration would enhance susceptibility and that administration of estrin would heighten resistance, was that each procedure affected susceptibility.

Later experiments^{3d} showed that the injection of estrogenic substance into castrate female monkeys enhanced resistance to intranasal instillation of the virus, these animals not only developing experimental poliomyelitis with less frequency than the controls, but the interval from the first instillation of virus to the onset of the disease was comparatively longer.

It is not known whether, on the one hand, the experimental conditions are optimal, or whether, on the other hand, they are entirely

artificial and beyond the bounds of what could exist in individuals exhibiting the manifestations seen in the suspected poliomyelitis susceptible type. However, since the experimental observations are consistent with epidemiologic implications, it is believed that the artificially induced conditions may be considered as reflecting those which exist in individuals susceptible to poliomyelitis.

Comparative urinary estrogen assays were done on poliomyelitis patients and control individuals at the Massachusetts Hospital School for Crippled Children, Canton. Urinary specimens were collected in a uniform manner from poliomyelitis patients and others of the same ages, and estrogen assays made by benzol extraction¹⁷ and titration by the vaginal smear method.²⁴

These assays were made on chronic cases, so the status at the time of the test does not necessarily reflect the condition of the patient at the time of the attack of poliomyelitis, which in these individuals had been from 1 to 20 years previously. Neither is there anything to show that the endocrine condition indicated is not a sequela to poliomyelitis. However, in view of epidemiologic considerations, we are inclined to interpret the results as reflecting a physiologic condition which already existed at the time of the attack, although the figures cannot be considered conclusive because of the wide range of variability between individuals even of the same age. In view of the enhanced resistance to intranasal instillation of the virus observed in castrate monkeys treated with estrogen, the finding of a higher average excretion of estrogenic substance in the group of poliomyelitis patients suggests the possibility that the endocrinopathy sought as the basis of autarceologic susceptibility does not lie in a simple deficiency in the elaboration of estrogenic substance, but rather in some discrepancy in its economy.

Obviously, a great deal of research must be carried on before a satisfactory solution will be obtained to the problem of urinary assays for sex hormones. Gustavson and D'Amour¹⁴ have recently reviewed the difficulties of the methods of assay. They point out that estrone (theelin) and estriol (theelol) are found in human urine almost entirely conjugated with glycuronic acid. The glycuronides must be hydrolyzed by acidifying the urine and heating before the estrogens can be extracted with immiscible solvents. Long boiling results in destruction of the estrogens. A compromise therefore has to be established between complete hydrolysis and minimum destruction.^{13,15} Marrian²⁰ adjusted the pH to about 1 and then heated the material in an autoclave at 120° C. for 2 hours.

It is of the utmost importance to repeat various methods of assay for total estrogenic content in exactly the manner reported by the original author if the results are to be comparable. Furthermore, the separation of the different estrogens before assaying the extract would give much more fundamental data.

In assaying androgens, the period of boiling must be limited to 15 minutes if losses by destruction are to be avoided.²¹ The problem of assaying the crude extract from urine is fraught with many difficulties.²

During the period in which the author has been engaged in the study of poliomyelitis, now extending over 25 years, he has had many

opportunities such as pointed out by Draper as "almost essential to be powerfully impressed by this quality of the human being" and has come to agree that patients with poliomyelitis tend to be of a different stripe than other individuals.^{3d} Although supported only in part by actual measurements,^{3c,10} the impression is that the characteristics of such a type are discernible in cases of poliomyelitis, most often in older boys and least often in younger girls.

But in this day of tests, measurements and assays, with insistence on statistical proof, clinical impressions lack convincingness. Measurements are too involved for general workability. Endocrinologic assays are not yet sufficiently seasoned for practical application. A test of the clinical impression itself, which at least has the advantage of being workable, is a simple numerical count of the frequency with which it is possible to select correctly the certain type of individual in which poliomyelitis occurs. We have attempted by this means to return to the basic question: Are those individuals attacked by poliomyelitis of a different stripe?

Observations have been made of 1,004 patients or photographs of patients with various crippling conditions, and those who appeared to be of the type prone to paralytic poliomyelitis have been separated from the others. The data represent 19 cases of poliomyelitis and 31 cases of other crippling conditions seen at the Shriner's Hospital, Springfield, Mass., in 1941; and 243 photographs of 177 cases of poliomyelitis, and 711 photographs of 520 cases of other crippling conditions admitted to the Massachusetts Hospital School for Crippled Children, Canton, Mass., from 1913 to 1941. Where more than one photograph of a case was available, readings were made at separate times, and with no knowledge of previous inspection. That the readings are not haphazard, but represent a selection of characteristics seen in the photographs is shown by the fact that, in a high percentage of the cases, second, third and sometimes even fourth photographs of the same individual were given the same reading, both where the selection was right and where it was wrong. In relatively few instances, subsequent readings on photographs were reversed.

Where the patients themselves were seen, all manifestations of the disease, for example a paralyzed arm or leg or an amputation, were entirely concealed. In the photographs, the whole was covered except the face. Inspection of photographs of face only is probably a severe test as to whether or not a selection can be made between the types of individuals having poliomyelitis and those with other crippling diseases: first, because some of the living form and expression is doubtless lost in a photograph, and, secondly, because body configuration is also in considerable part the basis of the clinical impression.* As a matter of fact, the comparatively higher proportion of correct selections among the patients who were seen indicates that there is something in the living ensemble which may not be evident in a photograph of the face.

The results of attempts to differentiate "poliomyelitis type" indi-

* After the readings herein recorded were completed, as a test a few erroneous readings given in the paper were made correctly when the body was exposed to view, and in a few instances where the type was particularly striking, patients recorded as admitted for other diseases were determined to have also had poliomyelitis.

viduals from patients with other crippling diseases are given in Table 1 by sex and age groups. It may be seen that inspection of patients themselves (Springfield group) resulted in a fairly sharp division. When photographs were used (Canton group) the selection was not as high, although the picking of the "poliomyelitis type" shows a positive correlation with the individuals who actually were patients with poliomyelitis in all of the age groups except girls under 10 years.

TABLE 1.—DIFFERENTIATION BY FACIAL CHARACTERISTICS BETWEEN INDIVIDUALS WITH POLIOMYELITIS AND OTHER CRIPPLING CONDITIONS.

		No. of tests.	Results of tests.													
			Total.	Males.						Females.						
				All.		10 yrs. and over.		Under 10 yrs.		All.		10 yrs. and over.		Under 10 yrs.		
		+	-	+	-	+	-	+	-	+	-	+	-	+	-	
Springfield	P	19	14	5	6	3	4	3	2	0	8	2	5	0	3	2
	NP	31	8	23	4	6	2	5	2	1	4	17	3	7	1	10
Canton	P	243	90	153	46	84	32	48	14	36	44	69	33	42	11	27
	NP	711	169	542	79	319	43	194	36	125	90	223	46	148	44	75
Total	P	262	104	158	52	87	36	51	16	36	52	71	38	42	14	29
	NP	742	177	565	83	325	45	199	38	126	94	240	49	155	45	85
Total		1004	281	723	135	412	81	250	54	162	146	311	87	197	59	114

P = Poliomyelitis.

NP = Other crippling conditions.

+

- = Facial characteristics not associated with poliomyelitis.

Springfield = patients seen.

Canton = photographs of patients seen.

The method of selection is open to the criticism, of course, that such a test is the actual reading of some result of poliomyelitis. It is often pointed out, for instance, "They are fat because they are in a wheelchair." The objection that the decisive characteristics in the poliomyelitis cases are not merely results of the attendant physical handicap is met, at least to some extent, by the fact that the control groups comprised equally physically handicapped individuals.

That characteristics which tend to be associated with poliomyelitis have been picked, rather than those accompanying or resulting from any of the other crippling diseases rejected, is shown by the fact that the percentage of selection of persons of the poliomyelitis type in the poliomyelitis group was 39.7 %, while for the five other groups the figure fell to between 18.2 and 26.6 % (Table 2). In other words, the differentiation was approximately equal in all of the groups of other crippling conditions.

It might well be suspected that in some instances actual effects of the disease formed the basis of differentiation, as for example particularly the group classified as "spastic." However, in all of the non-poliomyelitis groups the percentage of differentiation was lower. It should be stated that, whenever there was apparent evidence of disease

which could not be hidden, the cases were excluded by Dr. Nelson Hatt of the Shriner's Hospital, Springfield, and by Dr. John E. Fish, of the Massachusetts Hospital School for Crippled Children, Canton, and their staffs, and were not included in this study.

TABLE 2.—DIFFERENTIATION BY FACIAL CHARACTERISTICS BETWEEN INDIVIDUALS WITH POLIOMYELITIS AND OTHER CRIPPLING CONDITIONS BY DISEASE GROUPS.

	No of tests	Results of tests.															
		Total.				Males.						Females					
						All		10 yrs and over.		Under 10 yrs		All		10 yrs and over.		Under 10 yrs	
		+	-	%+	+	-	+	-	+	-	+	-	+	-	+	-	+
Poliomyelitis	262	104	158	39.7	52	87	36	51	16	36	52	71	38	42	14	29	
Congenital deformities	149	36	113	24.2	17	52	5	18	12	34	19	61	8	37	11	24	
Tuberculosis	124	32	92	25.8	15	58	10	38	5	20	17	34	12	24	5	10	
Osteomyelitis	83	15	68	18.1	8	57	6	49	2	8	7	11	7	10	0	1	
Spastic paralysis	82	17	65	20.7	8	32	5	17	3	15	9	33	3	16	6	17	
Rickets	68	15	53	22.1	3	27	0	6	3	21	12	26	2	15	10	11	
Obstetrical paralysis	18	4	14	22.2	0	8	0	6	0	2	4	6	1	3	3	3	
Miscellaneous	218	58	160	26.6	32	91	19	65	13	26	26	69	16	50	10	19	

+ = Facial characteristics suspected as being associated with susceptibility to paralytic poliomyelitis

- = Facial characteristics not associated with poliomyelitis.

TABLE 3.—DIFFERENTIATION BY FACIAL CHARACTERISTICS BETWEEN INDIVIDUALS WITH POLIOMYELITIS AND OTHER CRIPPLING CONDITIONS DEGREE OF CORRECTNESS ACCORDING TO AGE AND SEX

	No of tests	Results of tests															
		Total.				Males.						Females					
						All		10 yrs and over		Under 10 yrs		All		10 yrs and over		Under 10 yrs	
		R	W	R	W	R	W	R	W	R	W	R	W	R	W	R	W
Poliomyelitis	262	104	158	52	87	36	51	16	36	52	71	38	42	14	29		
Non-poliomyelitis	742	365	377	325	83	199	45	126	38	210	94	155	49	85	45		
Total	1004	669	335	377	170	235	96	142	74	262	165	193	91	99	74		
Per cent R		66.6		68.9		71.0		65.7		63.9		68.0		57.2			
Per cent + in total*		28.0		24.7		24.5		25.0		31.9		30.6		34.1			
Per cent poliomyelitis in group		26.1		25.4		26.3		24.1		26.9		28.2		24.9			

R = ...
W = ...
* = ...
... agreed with actual diagnosis
... did not agree with actual diagnosis
... in poliomyelitis and non-poliomyelitis groups selected as having the characteristics associated with susceptibility to paralytic poliomyelitis.

In Table 3 are shown the various groups by sex and age, according to "right" or "wrong" selection. It may be seen that the percentage of cases of poliomyelitis was approximately the same in all of the groups. The degree of correctness of selection was highest in boys 10 years of age and over; then, in order, in boys under 10 years, in girls 10 years and over, and lowest in girls under 10 years. Thus, the chances of a correct selection vary with the different age groups because of the assignment of different proportions of cases to the type in question. As may be seen from the table, the actual outcome shows that for boys 10 years and over, the correctness of the selection may be represented as 71%; for boys under 10 years, 65.7%; for girls 10 years and over, 68%; as compared with 57.2% for girls under 10 years. Thus, in all groups except younger girls, where the figures correspond with chance distribution, a partial distinction was made between poliomyelitis and other crippling conditions by this method; and in males and females over 10 years of age, it was "statistically significant."

Conclusions. Observations have been made on 1,004 patients or photographs of patients with various crippling conditions, to test the selective occurrence in certain types of individuals. The significant proportion of correct readings obtained confirms this impression and verifies Draper's concept of a "poliomyelitis type,"^{9a} as well as anthropometric studies indicating a difference in bodily measurements from the normal.^{3c,10} They are additional evidence in support of the epidemiologic observation that the frank disease tends to occur in but a limited and selected fraction of those exposed; they are consistent with the evidence presented elsewhere that these individuals are possessed of an autarceologic susceptibility,^{3b,c} as shown by the tendency of the disease to familial aggregation,⁴ and that the character in question is a physiologic difference of an endocrine nature^{3c} which, although to a considerable extent subclinical, manifests itself in the clinically discernible characteristics of the individuals: to a slighter degree in younger girls, moderately in younger boys and older girls, and to a still greater degree in boys 10 years of age and over.

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CORRECTION.—In their review "The Trivalent Arsenicals in Syphilis" (AM. J. MED. SCI., 201, 611, 1941) Stokes and Beerman (p. 622), erroneously state that Young and McClendon quote Goldman "as rating Mapharsen as immeasurably more effective than quinine in quartan infections, and notably more effective than arsphenamine and neoarsphenamine." It should read " . . . *tertian* infections."

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THE
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OCTOBER, 1941

ORIGINAL ARTICLES.

CLINICAL STUDIES WITH THE BALLISTOCARDIOGRAPH; IN
CONGESTIVE FAILURE, ON DIGITALIS ACTION, ON
CHANGES IN BALLISTIC FORM, AND IN
CERTAIN ACUTE EXPERIMENTS.*

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Work on the perfection of the ballistocardiograph¹¹ and the interpretation of its records has taken two directions. One of these might be termed the physiologic, the other the empirical approach. In the first it is aimed to discover what physiologic functions can be measured and how accurate the measurement is. This part of the work has consisted of a mathematical attack on the problems involved,^{7,11} animal experiments,¹¹ and comparisons of results obtained by the ballistocardiograph with those secured by other cardiac output methods;^{2,11} and work of this type is far from final completion. But, even if exact measurements could be made, it does not follow that the relationship between the physiologic aspects of the circulation and the clinical aspects of the cases would always be clear. Therefore, the empirical approach is equally important and this paper is a report of our progress in that direction. The data were drawn from over 1000 records made on many hundreds of patients during the last 5 years.

The purpose of this presentation is to acquaint readers with the characteristic appearance of ballistocardiograms in certain familiar clinical conditions, and with enough of the physiologic background to aid in drawing conclusions from such records. I propose to set forth the clinical possibilities of the method by showing how the results illuminate two questions much debated in recent years, the state of the circulation in congestive failure, and the

* A considerable part of the data contained in this paper was given, as a preliminary report, before the Association of American Physicians in May, 1941.

action of digitalis; and by demonstrating several approaches to new clinical problems which the ballistocardiograph makes possible.

The ballistocardiograph is simply a suspended table, braced to prevent motion in any direction but the longitudinal. Motion in that direction, opposed by a strong spring, is magnified by an optical system and photographed. A normal young adult lying on the table gives a record like that shown in Figure 1, Row 1, the main features of which can be easily understood. The contracting heart expels its blood headward initially and, for the same reason that when you fire a gun it kicks you in the shoulder, when the heart's blood goes headward the body is propelled feetward. An instant later this blood strikes the arch of the aorta and the curve of the pulmonary artery and its headward movement is in large part arrested and, simultaneously, blood in the thoracic and abdominal aortæ starts to move feetward. The forces now generated drive the body headward and one can easily see that the larger the amounts of blood expelled the greater would be the impacts. Large subjects give greater impacts than small ones and, if any subject submits himself to conditions known to stimulate cardiac output, such as exercise or adrenalin, a marked increase in the size of the recorded impacts follows invariably.

The view that the amplitude of the record is a function of the cardiac output is supported by these simple facts as well as by comparison with other cardiac output methods. Indeed, this is a field which, if foreign to clinicians and strange to physiologists, is an old stamping ground for physicists and engineers, the theory being directly derived from Newton's laws of motion. However, enough is known of the difficulties to make me believe that this

LEGEND FOR FIG. 1.

FIG. 1.—Ballistocardiograms reduced to one-half actual size and taken after a 15-minute rest period, never within 2 hours of a meal, with the subject horizontal. In the time record the largest intervals are 1 second.

Top. Record of a normal medical student. Age 23; height 5 ft. 10 in.; weight 155 pounds.

Rows 2 and 3. Records of S.S. Age 50, height 5 ft. 9 in., weight 125 pounds. Rheumatic heart disease, mitral stenosis and regurgitation, tricuspid regurgitation (?), auricular fibrillation. Row 2 while in failure; the large downward deflection at each end is diaphragmatic. Row 3 after recovery from it. This patient has been receiving digitalis for a long while and it was continued in the hospital.

Rows 4, 5 and 6. Records of C.J. Arteriosclerotic heart disease. Row 4, in failure. During Cheyne-Stokes breathing; time of ejection marked by dots under the record. Cardiac output per minute deviates from the expected normal by at least +22%. (Normal limits $\pm 22\%$.) Row 5, still in failure, during labored normal breathing; position of diaphragm noted on record; the large impacts are all diaphragmatic. Position of ejection indicated. Cardiac output -9%. Row 6, out of failure. Cardiac output +22%.

Row 7. M.C. Hypertensive heart disease. *Left*, while in failure; note the unusually prominent respiratory variations from the labored breathing. Cardiac output in middle of normal range. *Right*, patient out of failure with striking clinical improvement. Cardiac output -39%.

method, like most clinical methods, is of low accuracy and one should regard it in this way, contrasting its results not only with the ideal, but also with the ordinary clinical procedures which leave

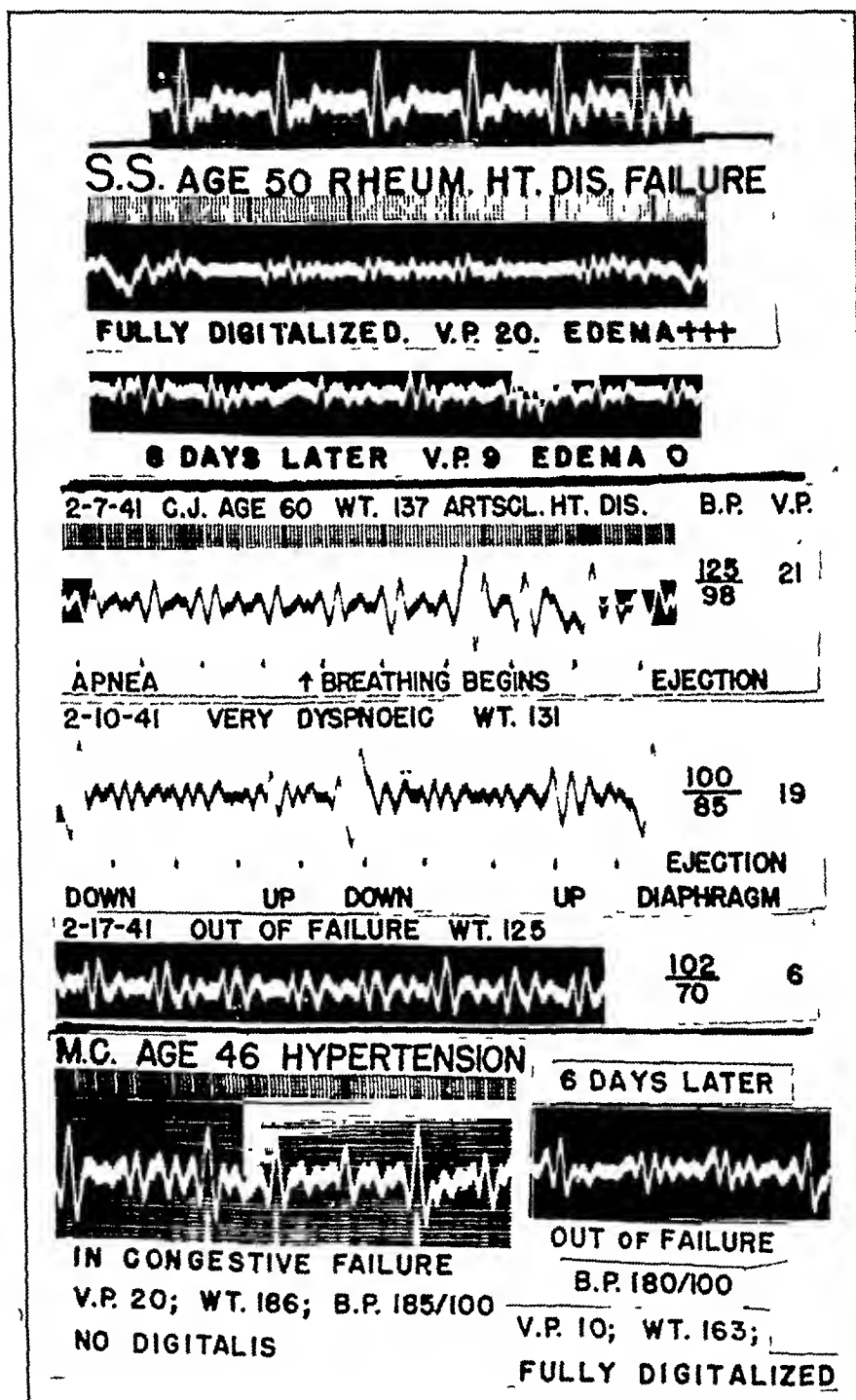


FIG. 1.

one with practically no idea at all concerning the amount of the circulation.

The method is well suited to use in the clinic. Nothing is required of the patient save that he lie relaxed on the table. No especial training is required of the operator and records can be secured in a few minutes. Indeed, the extremes of abnormality can often be identified by a glance at the flickering light spot.

Taking Records. All records were secured on subjects who had been lying at rest for at least 15 minutes. No record was taken within 2 hours after a meal.

On the Inspection of Ballistocardiograms. A chief hazard in the interpretation of the records by inspection alone, as readers would do, rather than by measurement and calculation, lies in the tendency to neglect the size and age of the subject. Large persons have far larger absolute cardiac outputs than small ones and the amplitude of the ballistic record is related to the absolute value, while the decision concerning normality depends on the output referred to the size of the subject. Also elderly subjects, even though healthy, give smaller impacts than their juniors. Also the heart rate is an important factor both directly, and indirectly by indicating a change in the duration of systole. Therefore to judge normality by a glance at the record requires considerable experience, even if age and weight are known, and direct comparison of the records of two subjects is handicapped by the same difficulties. However, records made by a single subject, at times reasonably close together, may be directly compared with confidence and in this paper the chief emphasis is on just such comparisons. So inspection should suffice the reader to justify, or reject, the main conclusions.

On examining the records, one must divest himself of a tendency, derived from experience with electrocardiograms, to concentrate attention on details. Any movement of the patient affects the ballistic record, so that artefacts are common. Only the features which are constantly repeated deserve any attention.

The *shape* of the record should engage attention first. The normal form (Fig. 1, Row 1) shows a sharp downward deflection (I wave) immediately followed by a sharp upward deflection (J wave) at each systole. These waves stand out in contrast to the smaller and more variable waves in diastole. There is evidence that the shape of the systolic record is a reflection of the changes in blood velocity in the aorta. The normal heart expels blood with a snap, *i. e.*, maximal velocity is attained early in systole, so in the normal ballistocardiogram the I and J peaks are sharp and they occur early in systole. In some diseased hearts the initial downward deflection (I wave) is inconspicuous and the J peak moves back in systole, changes consistent with the view that maximal expulsion velocity is not attained until late in systole in such cases.

The *size* of the record should be assessed next for, with reserva-

tions to be discussed, the amplitudes of the first downward and largest upward deflections, I and J waves, depend on the magnitude of the cardiac output. The respiratory variation is always present, unless the breath is held, the size of the complexes increasing during inspiration, diminishing during expiration. Cardiac output is estimated from measurements of representative high and low complexes.¹¹

In special circumstances other factors enter into the estimation of cardiac output from the size of the ballistic record. If the form is abnormal the evidence indicates that the cardiac output was larger than the amplitude of the ballistocardiogram suggests. When the rhythm is abnormal, uncertainty exists concerning the best value to use for the duration of systole, although I believe that this error will be small if data from several complexes are averaged.

In other cases the difficulties are inherent in the subject rather than the method. If the heart valves leak, the ballistocardiogram records the sum of the blood regurgitated and that contributing to the circulation, and this must be kept in mind in interpreting the records. In dyspneic patients the movements of the diaphragm create impacts which, if frequent and violent enough, may mask the cardiac complexes.

Indeed, all the difficulties are likely to be at their maximum in the investigation of advanced cardiac disease, which is a major subject in this presentation. Because of these various difficulties cardiac output cannot be estimated with confidence in several of the cases to be discussed. Nevertheless, the direction of the changes taking place in their circulation is obvious at a glance, and it is to these changes that I wish to direct attention.

Data on the Circulation in Congestive Heart Failure. This problem has always presented special difficulties. Methods of estimating cardiac output based on the use of gases are hazardous due to changing abnormalities in the lungs. The ballistic method avoids this difficulty but is subject to the others discussed before and they must be kept in mind when records are interpreted.

Figure 1 shows the record of S.S., a case of chronic rheumatic heart disease and mitral stenosis and regurgitation, and possibly tricuspid regurgitation as well. There was auricular fibrillation also and the records in Figure 1, characteristic of this condition, show the impacts irregularly spaced and varying somewhat in form from beat to beat.

In the first record the cardiac impacts are minute, the larger downward deflections at each end of the record are diaphragmatic impacts from the labored breathing; after improvement the latter are seen no more.

Recalling that, because of the regurgitation of blood through the leaking valves, the impacts would indicate a larger circulation than was actually present, one is left with no doubt that the circulation

during failure was far subnormal. After recovery from failure the impacts were larger. It is scarcely conceivable, especially in the absence of an active lesion or a change in physical signs, that a greater proportion of the blood was being regurgitated at this time, so we conclude that clinical improvement coincided with a return of the circulation towards normal.

A similar result was seen in patient W.F. (Fig. 2) who was in normal rhythm and without evidence of leaking valves, so his cardiac output can be estimated with more confidence. In his first record, obtained during congestion, the cardiac complexes can hardly be identified, the two large downward deflections being diaphragmatic. The contrast with later records, especially that obtained one year later, is striking. The circulation after recovery of his health was far larger than when he was seriously ill. I could cite many similar cases.

But exceptions are common. C.J. (Fig. 1) was also in normal rhythm and without evidence of leaking valves. This patient was in Cheyne-Stokes' respiration when first tested and the record shows the beginning of breathing after an apnea of about 20 seconds. The first breath was a small one but the coincident improvement in the circulation is very striking. During the larger and more forceful breaths which followed, the diaphragmatic impacts so distorted the record that estimation of cardiac output at that time was hazardous. Nevertheless, even during the apnea the circulation was not subnormal. In this instance congestive failure was not associated with subnormal circulation.

When clinical improvement began, the Cheyne-Stokes' breathing disappeared. The next record shows conspicuous diaphragmatic

LEGEND FOR FIG. 2.

FIG. 2.—Ballistocardiograms reduced to one-half actual size.

Rows 1 to 6. W.F., age 49, height 5 ft. 4 in. Admitted in congestive failure; the etiologic diagnosis was never clearly established. There was no evidence of valvular disease. Lues suspected, was never proved. The digitalis total dose is given in grains. Venous pressure is in cm. H₂O. Row 1, during failure, the large downward impacts are diaphragmatic; the cardiac complexes so small they can hardly be identified with certainty. He received a small dose of digitalis just before the record was made. Row 2, after rapid recovery from failure; note great increase in cardiac impacts and small dosage of digitalis. Row 3, the stimulation does not persist but clinical improvement continues. Row 4, an abnormality of form, the double I type, is present. Row 5, the record continues to improve, the larger complexes of the respiratory cycle are now normal, the smaller still abnormal. Patient was discharged the next day. Row 6, surprising improvement in record in a year's time. Patient is working steadily and considers himself cured.

Rows 7 and 8. M.B. Male. Age 20, height 5 ft. 5 in., weight 139 pounds. Traumatic arteriovenous communication right thigh, otherwise healthy. Row 7, before occlusion. Blood pressure 126/66. Cardiac output at normal average. Row 8, during occlusion of the circulation to the abnormal leg. Cardiac output -17%. Other control records obtained after release of the occlusion and during occlusion of the normal leg were very similar to that of Row 7 and have not been reproduced.

impacts from the regular labored breathing. Between them the cardiac impacts can be seen, smaller than in the previous record, but the cardiac output was still within normal limits. With com-

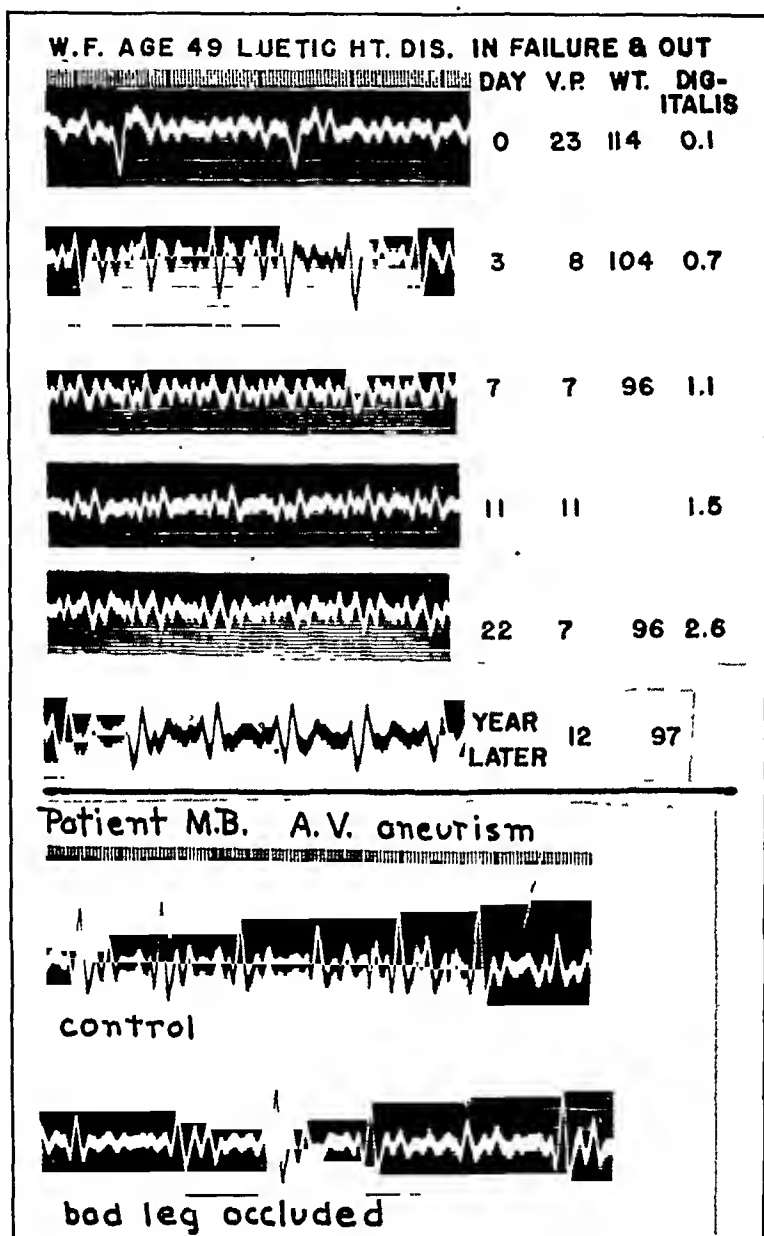


FIG. 2.

plete recovery from failure the circulation increased. If we had only the last two records we might conclude that clinical recovery was caused by the increase in circulation, but the evidence of the first record forbids this deduction.

In the case of M.C. (Fig. 1), the evidence is clear that his cardiac output during congestive failure was much larger than that present after he had recovered from it.

Equally impressive is the fact that many patients with profoundly subnormal circulations due to many causes do not have congestive failure. Cases I.P. (Fig. 3) and S.L. (Fig. 5) are examples.

In summary, our evidence concerning the circulation in congestive failure coincides with the great bulk of data in the literature. The majority of such cases have subnormal circulations, and improvement of the circulation often coincides with clinical improvement, as repeatedly found by Stewart.¹³ On the other hand, this relationship is not invariable, as emphasized by Harrison,⁴ and any idea that the symptoms are the direct mechanical consequence of a diminished circulation must be abandoned.

Data on Digitalis Action. Patient I.P. (Fig. 3) had arteriosclerotic heart disease with auricular fibrillation without any evidence of valvular disease. She had never been in failure and had received no digitalis for over a month. On admission the cardiac impacts were so small that it is hard to be certain where systole was. A week in bed without digitalis resulted in some slight clinical improvement, and the systolic impacts can be seen a little more clearly at this time. Digitalis given for 3 days coincided with further clinical improvement and the record shows a very marked increase in the size of the impacts at that time. It should be noted that the amount required to produce this effect was less than that calculated to produce the drug's full effect; the clinicians in charge did not regard the patient as "digitalized" when the third ballistocardiogram was taken. The patient was certainly digitalized 2 days later when the fourth record was taken. At this time the pulse rate had diminished and the circulation was certainly smaller than it had been 2 days before, although probably larger than on admission. The conspicuous effect is the transient stimulation of the circulation early in the drug's action.

A similar transient stimulation, demonstrated after 0.7 gm. of digitalis in patient W.F., is seen in his second record (Fig. 2), although the deep downward "K" waves give the impression that the cardiac output is larger than is actually the case.

This early stimulant action of digitalis can be demonstrated frequently in both normal rhythm and auricular fibrillation, but by no means invariably. Since it is a passing phase of the drug's action, it is to be expected that the records would not always be secured at the right time. Transient stimulation of the circulation after digitalis has appeared occasionally in tests with the older cardiac output methods in the hands of Stewart,¹² Harrison,⁴ and our own group;¹⁰ but, in the belief that digitalis had no effect until larger doses had been administered, most of the experiments were not timed to demonstrate it and it has never received the emphasis it deserves.

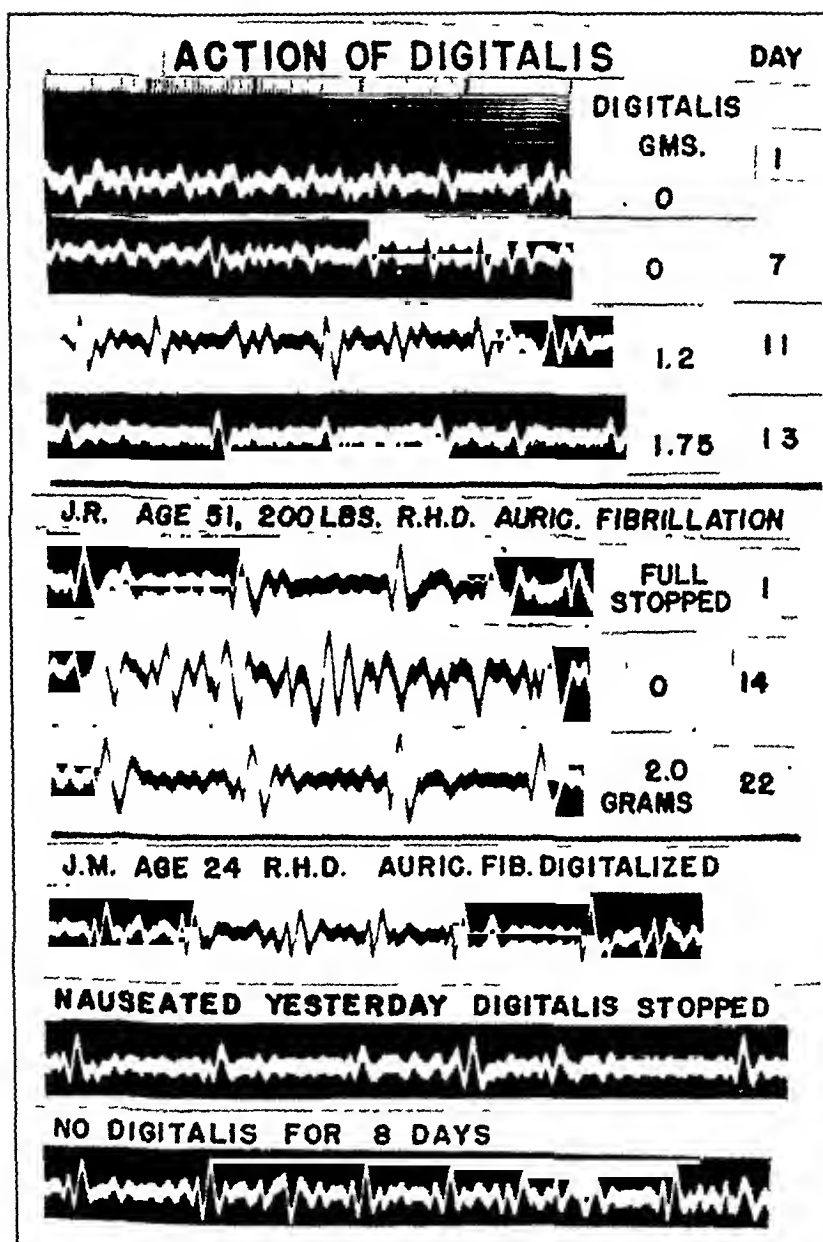


FIG. 3.—Ballistocardiograms reduced to one-half actual size. The top time record, largest interval 1 second, applies to all records.

Rows 1 to 4. Records of J.P., age 65, height 5 ft. 2 in., weight 128 pounds. Arteriosclerotic heart disease. Auricular fibrillation, Class II A. On admission the patient had had no digitalis for over a month. There were no signs of failure, but the patient was weak. Some weeks later operation disclosed a hypernephroma. The digitalis column gives the total dose administered.

Rows 5 to 7. J.R., age 51, height 5 ft. 10 in., weight 200 pounds. Rheumatic heart disease, mitral stenosis, auricular fibrillation, Class II A. No signs of failure. Fully digitalized on admission, the drug was omitted for 14 days, then given once more. There was no obvious change in his clinical condition during this test. Note the distorted record when not under the influence of the drug.

Rows 8 to 10. Records of J.M., age 24, height 5 ft. 9 in., weight 130 pounds. Rheumatic heart disease, mitral stenosis, auricular fibrillation. Row 8, Jan. 4, just recovered from congestive failure, fully digitalized and on maintenance dose. Row 9, Feb. 6, giving signs of too much digitalis. Row 10, Feb. 12, after 8 days without the drug.

When too much digitalis is given, the ballistocardiograph demonstrates that the well-known slowing of the rate is accompanied by a diminished size of the individual complexes (J.M., Fig. 3), a combination which must result in a profound depression of the circulation.

Finally, full or excessive dosage of digitalis has a characteristic effect on the ballistocardiograms which one can often identify at a glance. If the patient has auricular fibrillation the drug causes conspicuous flattening of the diastolic part of the ballistic record between the prominent systolic complexes. The records of patient J.R. (Fig. 3) digitalized, taken off the drug and then digitalized again, show this phenomenon well and it can be seen in the records of I.P. and J.M. (Fig. 3) also.

We find, therefore, that the action of digitalis consists of a stimulation early in its action at a time before the most obvious clinical effects can be recognized. This phase is temporary and it is followed by a period when slowing is prominent if there is auricular fibrillation. Overdosage is characterized by a profound depression of the circulation. Perhaps readers will find the initial stimulation surprising, for it has often been taught that the drug has no detectable effect before the full picture of digitalization sets in. But pharmacologists would be less surprised, for the stimulation demonstrated by our records is analogous to Cushny's first stage of digitalis action,³ the transient stimulation seen so often in acute animal experiments.

Studies on the Course of Disease. An example of our studies of this kind is given by the records, in Figure 4, of A.D., a young girl with rheumatic heart disease and mitral stenosis but without a murmur suggesting regurgitation. Admitted in her first attack of congestive failure, she had the subnormal cardiac output so often found in this condition. After 5 days of rest in bed without digitalis, diuresis occurred, the venous pressure fell and clinical improvement was marked without any corresponding improvement in the circulation. Indeed, when the venous pressure and weight had reached constant values the circulation was smaller than before.

The administration of digitalis resulted in a stimulation of cardiac output per minute before much of the drug had been given. The next day the patient went into auricular flutter which was not controlled by the small amount of digitalis then in the body; and the tachycardia increased the circulation to normal without any noteworthy change in the patient's symptoms. Continued administration of digitalis brought the ventricular rate under control 3 days later, the circulation becoming subnormal once more. After 6 days in flutter the rhythm changed to auricular fibrillation without any noteworthy change in ventricular function or cardiac output, as judged by the ballistic record. Three days later the patient complained of nausea and the ballistocardiogram record showed

the long pauses and flat diastole usually found when dosage of digitalis is excessive. It is to be noted that the slow rate carried the circulation far subnormal without any return of the congestive symptoms. Digitalis was withdrawn and improvement followed promptly.

Inspection of the records of Figure 4 draws attention to the similarity in the form and size of the systolic complexes throughout

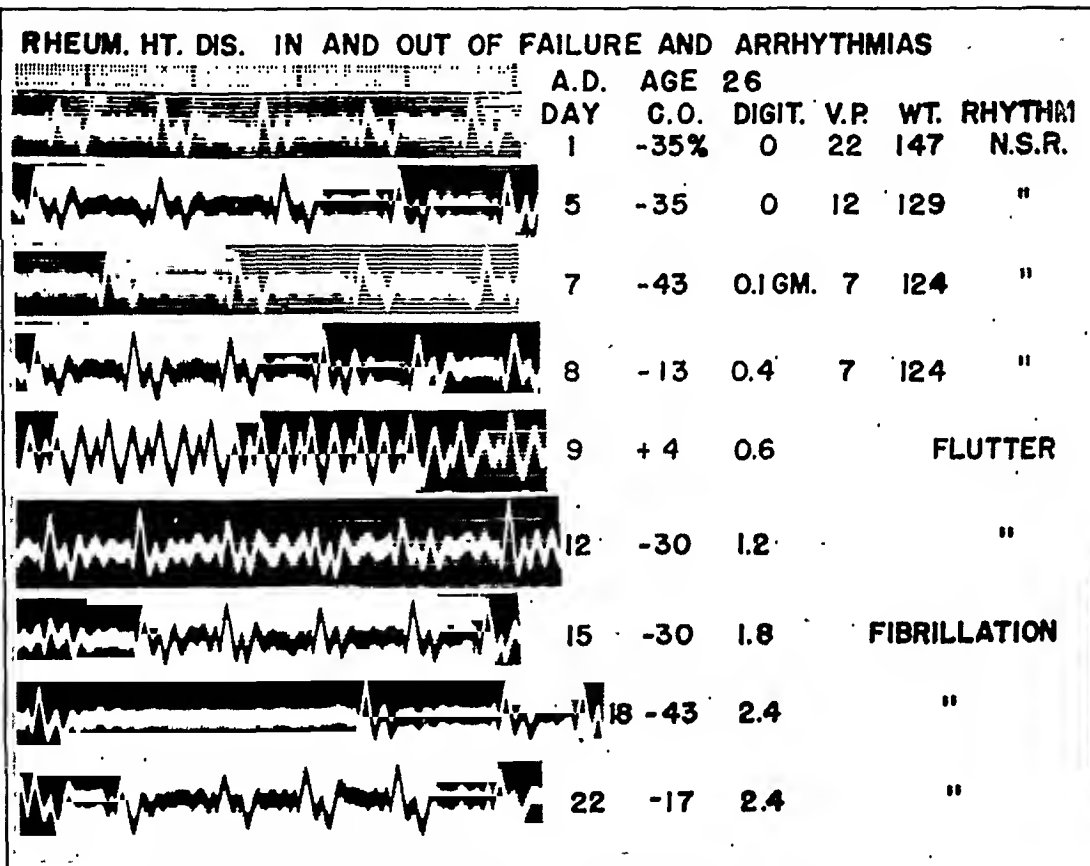


FIG. 4.—Records of A.D. Female. Age 26, height 5 ft. 2 in., weight 122 pounds. Rheumatic heart disease, mitral stenosis. Marked cardiac enlargement, orthodiagram +60% of expected normal. Blood pressure varied little from 100/70 except during rapid flutter (Row 5) when it was 80/65. Digitalis is given as the total dose; the patient had not received any before admission. The cardiac output is given in per cent of the normal average; the normal limits $\pm 22\%$.

the changing clinical picture. The stroke volume is quite constant and changes in the cardiac output per minute are almost entirely due to changes in rate of beating. Perhaps the cardiac disease has set a sharp limit on the stroke volume, and the patient's circulatory adaptations are largely limited to changes of rate. I have published the records of another case of rheumatic heart disease with mitral stenosis where the patient failed to show the normal increase in stroke volume after exercise.^{6a}

Another impressive fact is the magnitude of the changes of cardiac output per minute without any corresponding fluctuations in the patient's sensations or general condition. I could cite many other such instances.

The Ballistocardiogram in Acute Experiments. No exposition of this instrument would be complete without mentioning its utility in acute experiments. The ease and rapidity with which records can be secured, the fact that a continuous record can be obtained if desired, the additional fact that observation of the flickering light spot gives the operator a general knowledge of the course of events which permits proper timing of the photographs, combine to put the ballistocardiographic method in a class by itself for acute experiments on the human circulation. Records showing the effects of drug action,⁹ of artificial fever,^{6b} of exercise,^{6a} and of holding the breath^{6a} have been published, and we are still actively pursuing this field whenever clinical opportunity presents itself.

Records from another acute experiment are given in Figure 2. The patient had an arteriovenous fistula of the right leg secondary to a stab wound. The records were taken before and during compression of the abnormal limb by a blood pressure cuff until pulsation in the arteries was abolished. There was marked diminution in the circulation when the escape of blood through the fistula was prevented, as has been found repeatedly, in both clinical and experimental studies (for literature see Burwell *et al.*) In our subject additional records taken after release of the cuff and during similar occlusion of the circulation in the normal leg were almost identical with that obtained before occlusion, so they have not been reproduced.

LEGEND FOR FIG. 5.

FIG. 5.—S.L. Female. Age 48, height 4 ft. 11 in., weight 119 pounds. Severe angina pectoris. Records two-thirds actual size.

Top Row. Jan. 16, 1940. Soon after admission. Blood pressure 126/80. Cardiac output —52% (normal limits $\pm 22\%$).

Row 2. Jan. 22, 1940. Blood pressure 140/70. After block of left 2, 3, 4, 5 sympathetic ganglia without relief. Cardiac output —57%.

Row 3. Mar. 11, 1940. Ten days after release of common duct adhesions. Drain in common duct. Cardiac output —17%. Now within normal limits.

Rows 4 to 7. Concerned with the injection of saline solution down common duct.

Row 4. Time: 11.19. Before injection. Blood pressure 120/80. Duct pressure 150 mm. H₂O. Patient comfortable. Has had morphine, gr. $\frac{1}{4}$ s.c., recently. Cardiac output —22%.

Row 5. Time: 11.29. Fluid running in under 200 mm. H₂O head of pressure. Blood pressure 120/76. Cardiac output —43%. No pain yet. Note reduction of impacts.

Row 6. Time: 11.41. Blood pressure 130/80. Head of perfusion pressure 500 mm. Cardiac output —22% or higher. Squeezing precordial pain radiating down left arm. Perfusion stopped after this record. Note abnormal record form, the doubled point of the first downward deflection, the "double I" type.

Row 7. Time: 12.08. Blood pressure 120/80. Duct pressure 160. Cardiac output —30%. Patient comfortable. Form of record normal again.

Similar experiments have been performed on 2 other cases of traumatic arteriovenous communications. The effect of occluding

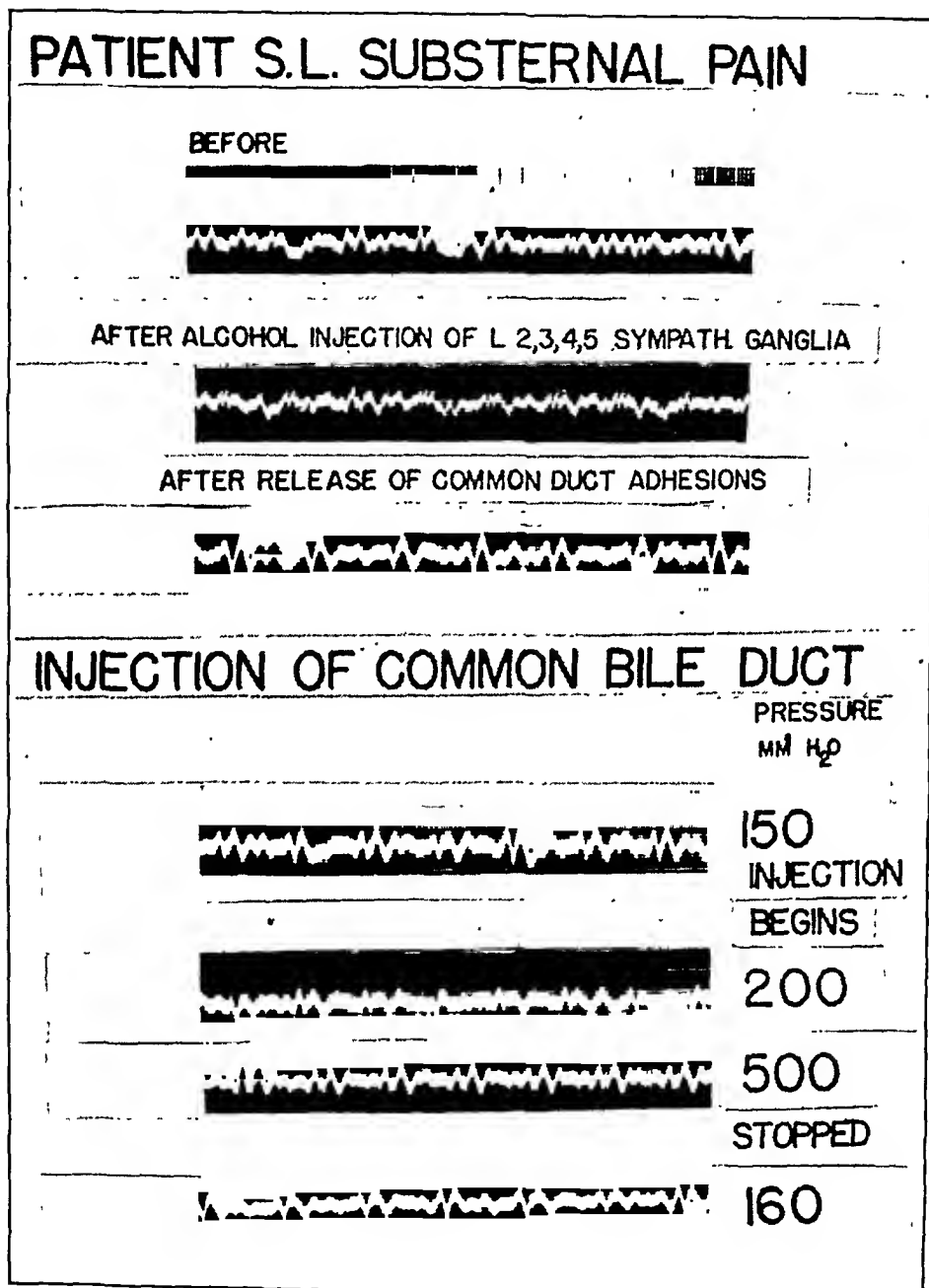


FIG. 5.

the communication has varied in the different cases and the experiment may well provide a convenient measure of the size of the abnormality.

Another acute experiment, which gave a most unexpected result, was performed with the help of Dr. H. P. Royster.⁸ Patient S.L. (see Fig. 5) had been bedridden for many months with attacks of pain resembling angina pectoris, an attack being brought on by 2 trips over Dr. Master's⁵ steps. At first the diagnosis had not been clear and 6 years before this admission the patient's gall bladder had been removed in the hope that this was the origin of the attacks. No relief had followed and since that time numerous operations on the sympathetic nerves had been attempted to relieve the intolerable situation. On admission to the hospital the record in Figure 5, Row 1, was secured, which indicated that the patient had a circulation only about one-half the expected normal, a finding common in severe coronary disease. Alcohol injected into sympathetic ganglia did not help; after this procedure the circulation was a little worse than before (Fig. 5, Row 2). It was to relieve a desperate situation that Dr. Ravdin attempted further common duct surgery. Adhesions were found, the common duct was freed and drained. After this operation the patient was very much better, although not entirely relieved of her attacks, and we were amazed to find that the circulation had greatly improved (Fig. 5, Row 3).

Two of Dr. Ravdin's assistants, Drs. Royster and Sanders, in pursuit of their interest in ascertaining the pressure in the common duct sufficient to open the sphincter, injected saline solution down the patient's drainage tube. To their surprise they produced an attack similar to those from which the patient had been suffering, and described as typical angina pectoris. They needed no persuasion to repeat the injection on the ballistic table (Fig. 5, Rows 4-7). The procedure not only caused pain but also marked transient depression of the circulation and an abnormality in the form of the impacts.

The pain the patient described was typical of angina pectoris but we do not wish to place too much emphasis on having caused

LEGEND FOR FIG. 6.

FIG. 6.--Changes in the form of the ballistic record induced by operative procedures in patients with abnormal hearts. Reproduced one-half actual size.

Rows 1 to 4. L.K. Malignant hypertension. Row 1, a normal form; cardiac output per minute -27% (subnormal); Row 2, note M-shaped records. Cardiac output over -22%. Row 3, diaphragmatic impacts = D, and ejection marked. Cardiac output -35%. Row 4, note recovery of normal form. Cardiac output -17% (normal).

Rows 5 to 7. G.T. Malignant hypertension. Row 5, normal form. Cardiac output +22% (normal). Row 6, form very abnormal. Cardiac output doubtful. Row 7, form has greatly improved. Cardiac output -13% (normal).

Rows 8 to 10. K.T. Angina pectoris and calculous cholecystitis. Row 8, normal form. Cardiac output -39% (very subnormal). Row 9, note change to abnormal form. Cardiac output uncertain. Row 10, return to normal form. Cardiac output -43%.

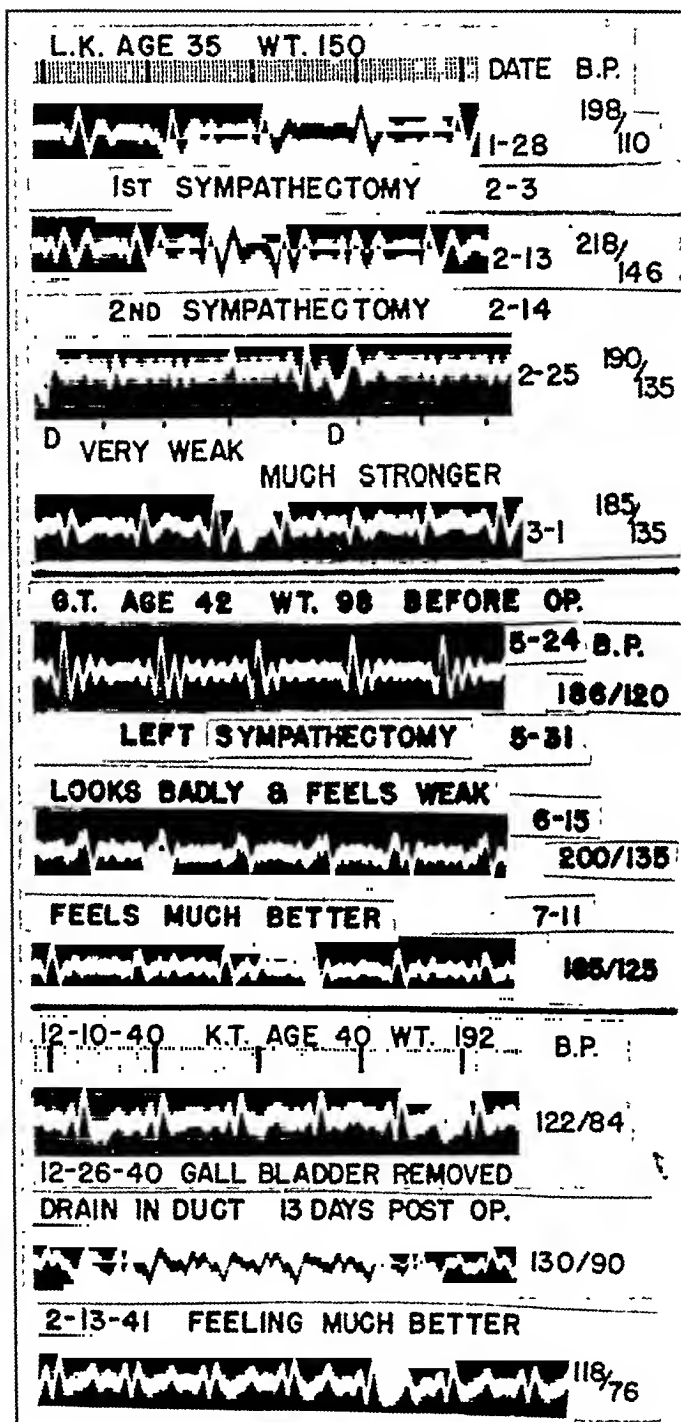


FIG. 6.

angina by distending the bile duct. The patient had suffered many things from many physicians. She had the suggestibility of the chronic invalid and she knew the story expected perfectly. But in the difference between the records there is an objective demonstration that there is something operating from the biliary passages which can depress the general circulation profoundly. This provides a definite physiologic background for the vague relation between hepatic and cardiac disease which is so often recognized by clinicians.

Changes in the Form of the Ballistic Record. The majority of the data presented before might have been attained by other cardiac output methods if a team of highly trained operators had worked for a long enough time. In such cases the advantage of the ballistocardiograph consists of its ease and rapidity of operation. But the ballistocardiograph may also demonstrate cardiac abnormality by alterations in the form of the ballistic record and so provide evidence of cardiac health or disease of a type not obtainable by any other method.

Abnormalities of the form of the complexes are common in persons with collateral evidence of serious heart disease, and, if present, they usually persist in spite of therapeutic measures. The records of 3 cases in which the distortion was temporary are shown in Figure 6. Each of these patients exhibited some collateral evidence of cardiac abnormality on admission and the ballistic abnormality was precipitated by an operation and disappeared as the patient recovered from its effects.

G.T. had essential hypertension and an enlarged heart. The cardiac output on admission and the ballistic form were both normal. After her first sympathectomy she recovered slowly from the effects of the operation and she looked badly and felt weak when the second record was taken. Compared with the previous record, the initial downward deflection, *I* wave, is shallower and more rounded; the upward peak, *J* wave, is flattened or split and much reduced in height. The time between the second downward deflection, *K* wave, and the beginning of ejection is prolonged. This is the form the ballistic record is expected to take when the ejected blood attains maximum velocity late rather than early in systole.

As this patient recovered, the form of the record returned to the normal. She underwent a second sympathectomy successfully and no ballistic abnormality was detected after it.

L.K., a second case of hypertension, had a heart whose silhouette area was 21% above the expected normal and a subnormal cardiac output per minute. After the first sympathectomy the records became M-shaped. After the second operation she was very weak; diaphragmatic impacts showed the labored breathing and the cardiac impacts were greatly reduced in amplitude. As she recovered, the ballistic form returned to normal. The changes of ballistic form

seen in this case are quite like some of those demonstrated in an acute experiment on an anesthetized dog subjected to asphyxia.¹¹

K.T. had angina pectoris and exhibited the subnormal circulation found so frequently in these cases. After removal of the gall bladder the ballistic form changed profoundly, the prominent upward deflection (*J* wave) being greatly reduced in size and the second downward deflection (*K* wave) moving far back in systole. As the patient recovered her strength the ballistic form returned to normal.

Records obtained on persons with normal hearts subjected to operations have not shown any ballistic abnormality during the postoperative period, but I have only a few data on the point.

Summary. This presentation is designed to demonstrate the utility of the ballistocardiogram as an instrument for the diagnosis of cardiac and circulatory abnormality and for the solution of certain clinical problems. Records are presented indicating changes in the circulation in congestive heart failure and on recovery from it, during digitalis action, and in various arrhythmias in one patient.

The method is especially suited for acute clinical experiments. The examples cited include ballistocardiograms from a case of traumatic arteriovenous communication before and during occlusion of the communication, and similar records from a patient with angina pectoris in whom pain was produced by the injection of fluid down a drainage tube into the common bile duct.

Changes in the form of the ballistic record provide evidence of cardiac dysfunction of a type not obtainable by other methods. The examples cited were obtained from 3 patients in whom the abnormality followed operative procedures, and disappeared as strength was regained.

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SYNOVIAL FLUID AND SYNOVIAL MEMBRANE ABNORMALITIES RESULTING FROM VARYING GRADES OF SYSTEMIC INFECTION AND EDEMA.*†

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For a number of years, this laboratory has been concerned with studies pertaining to the physiology of normal joints and the alterations produced by disease.^{†1,3,8-10} The present report, a continuation of previous work,³ was undertaken to correlate various degrees of systemic infection and subcutaneous edema occurring either separately or combined with abnormalities of synovial fluid and membrane.

Materials and Methods. Synovial fluid was aspirated as completely as possible from 156 knee joints of 103 postmortem cases and examined within 30 minutes of death. The techniques employed have been described.³ Long strips of tissue, including synovial lining and subsynovial tissue, were removed from the pouches lateral and medial to the patellæ of 49 joints. These specimens were fixed in Zenker's fluid and in 10% formalin. Representative blocks of tissue, including the external part of the capsule, were embedded in celloidin or paraffin. The cut sections were stained with eosin and methylene blue or hematoxylin and eosin. The degree and extent of edema were known from antemortem examination. The type, severity and duration of the infectious process were estimated on the basis of complete clinical and laboratory records and postmortem studies. The latter were complete in 53 instances. Patients having died from infection without demonstrable edema were divided into 3 groups according to the severity of the infection. Those with non-infectious diseases, evincing edema, were classified separately. When both infection and edema were present, the cases were grouped according to the severity of the infection. Terminal infections, sharply localized to one organ or system, complicating such disorders as carcinomatosis, cerebral hemorrhage, asthma, and so on, were designated as minimal. When the infection was more widespread, especially if bacterial metastases had occurred, it was classified as moderate.

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‡ Unpublished data.

The group with severe infection comprised cases with proved or presumptive septicemia. This classification is admittedly arbitrary and may have been based in some instances on an erroneous interpretation but offers an approximate and for the present purposes sufficient indication of the extent of the infectious process.

Accordingly, the 156 fluids were segregated into the following groups:

- I. 37 from cases with minimal infection without edema
- II. 24 from cases with moderate infection without edema
- III. 20 from cases with severe infection without edema
- IV. 18 from cases with edema, without infection
- V. 27 from cases with edema and minimal infection
- VI. 30 from cases with edema and moderate or severe infection.

Results. *Synovial Fluid Abnormalities.* It is evident from Table 1 that systemic infection and edema produce characteristic deviations from normal in the synovial fluid. The normal values used for comparison are taken from previously published data.³

TABLE 1.—VARIATIONS IN THE AMOUNT AND CELLULAR COMPOSITION OF SYNOVIAL FLUID RESULTING FROM VARYING GRADES OF INFECTION AND EDEMA.

Group.	Total No. of joints examined.	Clinical data.		Amt of synovial fluid, (cc.).	Nucleated cells in synovial fluid.								Synovial and unclassified cells.		Variations observed.
		Peripheral edema.	Degree of infection.		No. per c.mm.	Neutrophils		Macrophages		Lymphocytes					
						%.	Absolute.	%	Absolute.	%	Absolute.	%.	Absolute.		
Normal	20	Absent	Absent	0 13	13	0 0	0 0	0 0	0 0	6 0	1 7	0 0	0 0	Minimum	
				2 00	180	25 0	18 0	83 0	106 0	78 0	61 2	18 0	9 6	Maximum	
				0 45	63 2	6 5	3 3	62 9	41 7	24 6	14 7	5 6	3 5	Average	
I	37	Absent	Mild	0 13	4	0 0	0 0	20 0	5 3	0 0	0 0	0 0	0 0	Minimum	
				7 50	400	60 0	342 0	98 0	315 0	72 0	176 0	10 0	45 0	Maximum	
				1 20	152	17 9	37 7	55 4	74 3	26 5	33 1	2 9	4 0	Average	
II	24	Absent	Mod.	0 10	20	0 0	0 0	6 0	12 0	0 0	0 0	0 0	0 0	Minimum	
				4 50	9,500	94 0	6,650 0	84 0	2280 0	88 0	1003 2	20 0	44 4	Maximum	
				0 74	656	29 0	379 9	40 5	166 9	26 3	102 7	4 1	6 7	Average	
III	20	Absent	Severe	0 13	30	0 0	0 0	9 0	10 2	0 0	0 0	0 0	0 0	Minimum	
				8 00	8,850	90 0	7,965 0	93 0	796 5	42 0	542 0	8 0	97 5	Maximum	
				1 40	1,022	34 5	612 2	49 0	252 0	16 5	150 8	1 4	7 8	Average	
IV	18*	Present	Absent	2 00	1	0 0	0 0	4 0	1 0	0 0	0 0	0 0	0 0	Minimum	
				40 00	128	98 0	49 0	80 0	35 9	68 0	81 9	10 0	8 0	Maximum	
				10 70	32	22 1	9 2	51 9	13 6	23 9	12 8	1 6	1 7	Average	
V	27*	Present	Mild	0 40	6	0 0	12 0	4 4	0 0	4 0	0 6	0 0	0 0	Minimum	
				30 00	665	46 0	83 0	206 1	199 5	80 0	432 3	12 0	20 0	Maximum	
				5 30	75	9 4	6 5	57 4	37 4	30 2	33 7	2 0	2 3	Average	
VI	30	Present	Mod. and severe	0 33	13	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	Minimum	
				20 09	24,700	96 0	23,218 0	89 0	3159 0	84 0	390 0	12 0	183 6	Maximum	
				5 10	2,059	38 5	1,516 4	44 5	352 5	13 0	65 6	2 3	11 6	Average	

* Two synovial fluids in Groups IV and V did not have differential cell counts.

Amount of Synovial Fluid. The amount of synovial fluid aspirated from the 156 knee joints showed individual variations from 0.1 to 40 cc. as compared to minimal-maximal variations of 0.13 to 2.0 cc. and an average value of 0.45 cc. for normal adult knee joints (see Table 1 and Chart 1.)

From the figures below, it is apparent that increased amounts of synovial fluid were usually found in patients with edema, the common causes of which were cardiac failure, nephritis, lowered serum proteins, phlebitis and regional hypodermoclyses.

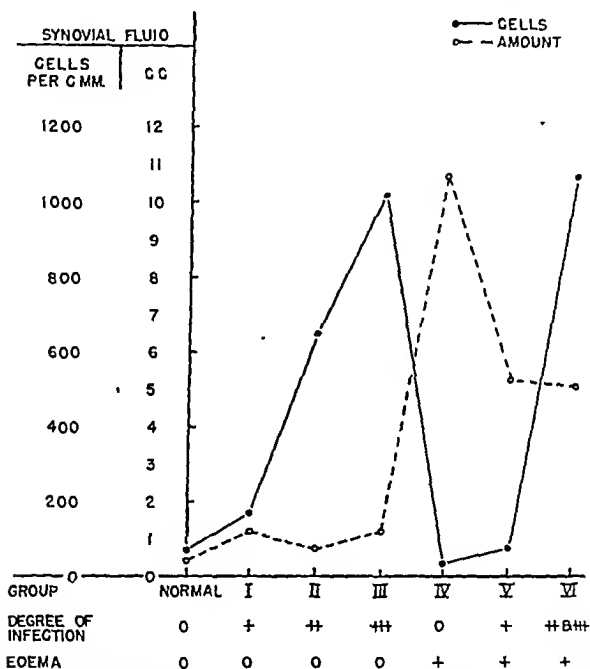


CHART 1.—The average amount of synovial fluid obtained from the knee joints of normal individuals and individuals dying with varying grades of infection and edema. The average total nucleated cell counts are likewise presented.

Synovial Fluids Obtained from Edematous Patients. Of 75 specimens, 25 were less than 2 cc. in amount, 15 were between 2 and 5 cc., and 35 were more than 5 cc. The majority of these fluids had a normal cytology. Of 50 specimens, each amounting to more than 2 cc., from patients with recognizable edema, 11 showed an increased number of nucleated cells, and 14 had an elevated neutrophil count. Of 12 specimens surpassing the normal quantity, 7 were derived from patients without demonstrable edema but minimal infection and showed normal cytology, whereas 5 from non-edematous individuals with some infections proved to have increased cell counts. The largest effusions, 20 to 40 cc., were aspirated from patients with cardiac edema. In such cases, the fluid content of the two knees

was practically the same. These findings suggest that the physiologic alterations⁵ responsible for the various types of edema resulted in an increased transudation into the joints. That such increased amounts of synovial fluid consisted largely of plasma water is attested to by low nucleated cell counts, reduced viscosities and lowered content of total solids, protein and mucin.⁹

The amount of fluid obtained from patients dying with infection was generally less than 2 cc. unless edema was present. Of 81 synovial fluids obtained from patients with infection but without edema, 69 were 2 cc. or less, 12 were more than 2 cc. Most of these

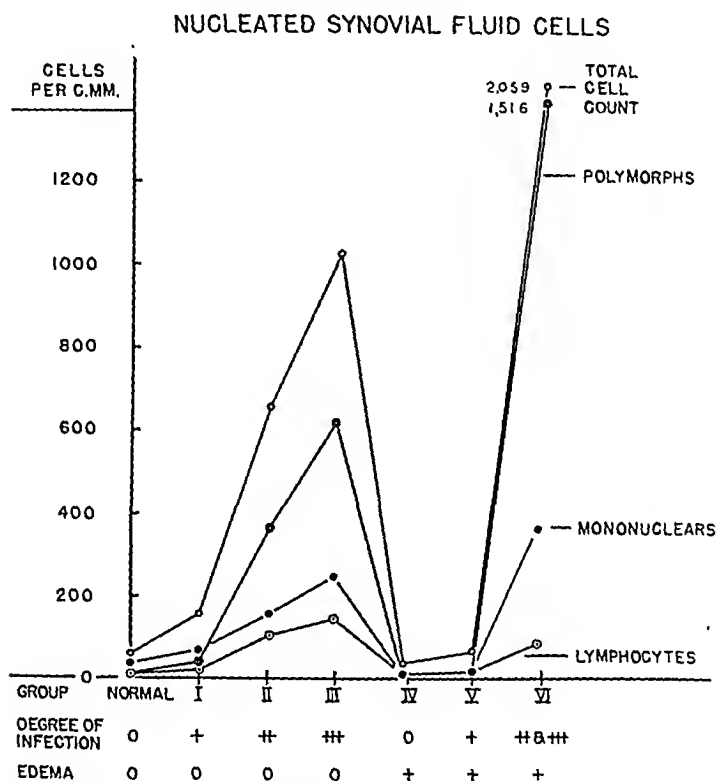


CHART 2.—The average total nucleated cell, neutrophil, mononuclear and lymphocyte counts of normal human synovial fluid and of synovial fluids obtained from patients dying with varying grades of infection and edema.

specimens showed cytologic abnormalities. Increased amounts of synovial fluid were present in 20% (4 fluids) of 11 patients with severe infection alone, but in 70% (21 fluids) of 17 individuals who showed both moderate or severe infection and edema. These observations indicate that although inflammation of the synovial tissues was frequently present in patients with infection, usually it was not of sufficient grade to permit increased transudation into the joints.

Total Number of Nucleated Cells and Individual Cell Types. The total nucleated cell counts of normal human fluid specimens range

from 13 to 180 with an average of 63 per c.mm. (Table 1.) The cell types are expressed as percentage figures and absolute counts, since the latter method portrays more accurately the cellular constituents. The percentages and absolute numbers of cells per c.mm. in normal fluid are: 62.9% or 41.7 macrophages, 24.6% or 14.7 lymphocytes, 6.5% or 3.3 neutrophils, 4.3% or 2.5 synovial cells and 2.2% or 0.8 unidentified cells. Neutrophils range from 0 to 25%, the absolute counts from 0 to 18. In the analysis of the present data, a total nucleated cell count of over 180 and an absolute neutrophil count above 18 are considered normal.

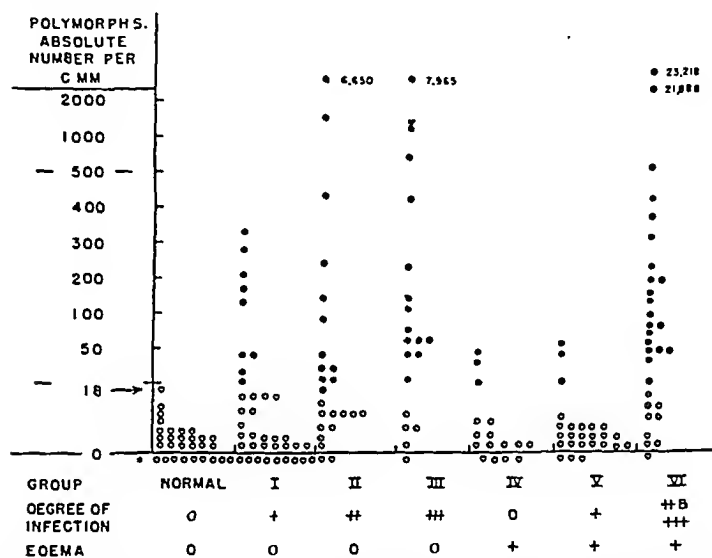


CHART 3.—Shows the number of synovial fluids in each group which contained an increased number of neutrophils, the established normal being 18 per c.mm. The values listed below the base line (*) represent fluids that contained no neutrophils. Only 16 of the 18 fluids in Group IV and 25 of the 27 fluids in Group V had differential cell counts; therefore only 181 dots appear on this chart.

As can be seen from Table 1, the total nucleated cell counts in the present series varied from 1 to 24,700. The highest counts were observed in cases with both severe infection and edema (Group VI), the next highest in the fluids obtained from patients with severe infections but no edema (Group III), and the lowest in the group showing edema only (Group IV). Chart 2 shows that the elevated total cell counts were due chiefly to increases in the neutrophils. The highest neutrophil count, 23,218 (84%), was found in a fluid having a total cell count of 24,700 (Case 24, Table 2). This specimen was obtained from a patient dying from a ruptured appendix and a complicating hemolytic streptococcus septicemia. The number of fluids in each group that had an increased number of neutrophils is readily seen in Chart 3.

ANALYSIS OF TOTAL NUCLEATED AND NEUTROPHIL COUNTS.

Number of fluids.	Type of case.		Number with increased total nucleated cell counts.	Number with increased neutrophils.
	Infection.	Edema.		
81	+	0	30	36
57	+	+	21	24
18	0	+	0	3

From the above table it will be apparent that 63 of the 156 fluids had increased absolute neutrophil counts as compared to 51 with elevated total nucleated cell counts.



FIG. 1.—Normal synovial lining tissue (from the right knee of Case 8, Table 2, Group I). (Orig. mag. $\times 310$.) This patient died of thyrotoxicosis, diabetes mellitus and bronchopneumonia. The synovial fluids obtained from the knees of this patient were normal. (Section stained with hematoxylin-eosin.) (Small numbers of leukocytes are usually found if sufficiently large areas of the synovial membrane and subsynovial tissues are examined. The presence of 1 to 3 leukocytes per field ($\times 900$) was not considered abnormal unless found in most of the fields examined, or accompanied by perivascular accumulations in the subsynovial tissue.)

Correlations of Synovial Fluid and Synovial Membrane Abnormalities. In order to obtain further information concerning the significance of the synovial fluid abnormalities, synovial tissue specimens were examined microscopically and the degree of cellular infiltration in representative oil immersion fields ($\times 900$) was recorded. Note was made of the approximate number of neutrophils, mononuclears, lymphocytes, plasma cells and the presence or absence of perivascular inflammatory cell accumulations. The degree of inflammation present was recorded as none, minimal, moderate and severe. The synovial fluid findings, the clinical data and histologic studies presented in Table 2 were not compared with one another until the microscopic sections had been described.

TABLE 2.—POSTMORTEM OBSERVATIONS OF THE SYNOVIAL FLUID CYTOLOGY AND SYNOVIAL MEMBRANE FROM INDIVIDUALS WITH VARYING DEGREES OF INFECTION.

Case No.	Group No.	Peri-pheral edema.	Degree of infection.	Knee.	Ant. of syn-ovial fluid (cc.).	Nucleated cells in synovial fluid.										Synovial membranes.		Blood leukocyte count (in thous.).	Postmortem cultures.		Anatomic diagnoses.
						Total No. per cu. mm.	Neutrophils.		Macrophages.		Lymphocytes.		Synovial and unclassified cells.		Nor-mal.	Ab-nor-mal.	Synovial fluid.		Blood.		
							%	Abso-lute.	%	Abso-lute.	%	Abso-lute.	%	Abso-lute.							
1	Normal	0	0	R L	0.20 0.50	20 50	25 20	5.0 10.0	0	0.0	0	0.0	05 60	13.0 30.0	10 10	2.0 5.0	Not done Not done	No growth No growth	Not done Not done	Chr. hem. 51 hr. before death.	
2	I	0	+	R	7.00	4	0	0.0	66	2.6	34	1.4	0	0.0	13.8	Not done	Not done	Not done	Bronchogenic carc. with gen. metas-tasis; chr. pneu., rt. up. lobe.		
3	I	0	+	R L	0.13 0.13	20 30	10 10	2.0 3.0	80 60	10.0 18.0	10 30	2.0 9.0	0 0	0.0 0.0	10.0 10.0	Not done Not done	Not done Not done	Not done Not done	Carc. of stom. with perf.; subphrenic abscess; peritonitis; bilat. br. pneu.		
4	I	0	+	R L	2.50 5.00	40 30	40 50	16.0 15.0	0 0	0.0 0.0	60 50	21.0 15.0	0 0	0.0 0.0	16.7 16.7	Not done Not done	Not done Not done	Not done Not done	Bronch. asthma with asphyxia; ac. uncoap. bronchitis; chr. pleuritis; pericarditis.		
5	I	0	+	R L	0.50 0.30	315 185	0 2	0.0 3.7	100 98	315.0 181.3	0 0	0.0 0.0	0 0	0.0 0.0	16.0 16.0	Not done Not done	Staph. aureus Staph. aureus	Dissect. aneurysm of aorta with rup-ture into pericardium; ac. central necrosis of liver.			
6	I	0	+	R L	0.50 0.50	60 50	0 4	0.0 0.0	50 72	33.0 30.0	40 20	24.0 10.0	4 4	2.4 2.0	33.6 33.6	Not done Not done	B. coli B. coli	Retropertitoneal abscess (B. coli); bronchopneum.			
7	I	0	+	R L	0.50 0.50	400 400	30 40	120.0 160.0	20 20	104.0 80.0	44 40	170.0 160.0	0 0	0.0 0.0	15.4 15.4	No growth No growth	Not done Not done	Epidermoid carc. of lung; broncho-pneum.; chr. pleuritis.			
8	I	0	+	R L	0.20 0.20	80 10	50 40	45.0 4.0	24 40	19.0 4.0	20 20	16.0 2.0	0 0	0.0 0.0	16.0 16.0	No growth No growth	Not done Not done	Bronchopneum.; diabetes mellitus; thyrotoxicosis.			
9	I	0	+	R L	0.50 5.00	50 30	50 25	25.0 7.5	25 0	12.5 0.0	25 75	22.5 0.0	0 0	0.0 0.0	13.4 13.4	Not done Not done	B. coli B. coli	Pemphigus.			
10	II	0	++	R L	0.50 0.50	60 35	10 30	21.0 10.5	48 53	28.8 18.5	10 9	0.0 3.0	2 3	1.2 3.0	0.0 0.0	Not done Not done	No growth No growth	Perforated appendix; gen. peritonitis; bronchopneum.			
11	II	0	++	R L	0.30 2.00	85 55	2 8	1.7 4.1	82 82	60.7 45.1	10 4	8.5 2.2	6 6	5.1 3.3	10.0 10.0	Not done Not done	No growth No growth	Ac. intestinal obstr.; peritonitis with multiple abscess; bronchopneum.; bi-lateral pleuritis; esoph. ulceration.			

12	II	0	++	R L	1 00 1 00	920 130	44 14	404 8 18 2	22 62	202 4 80 6	34 22	312 8 28 6	0 2	0 0 2.6	..	++	18 0 18 0	Not done Not done	No growth No growth	Bronchopneu.; pulm. infaret.; ac. bronchitis; carbon monoxide poi- soning; decubitus ulcers.
13	II	0	++	R L	0 50 0 50	9500 1,400	70 94	6,650 0 1,316 0	24 6	2280 0 84 0	6 0	570 0 0 0	0 0	0 0 0 0	.	++	15 0 15 0	Not done Not done	No growth No growth	Bilat. lobar pneu. (Type IV); bilat. ac. fibrinous pleuritis.
14	III	0	+++	R L	1 00 0 75	80 100	2 10	1 6 10 0	75 70	60 0 70 0	23 20	18 4 20 0	0 0	0 0 0 0	++	.	15 0 15 0	Not done Not done	Hem. strep. Hem. strep.	Peritonitis (post-cholecystectomy).
15	III	0	+++	R L	0 75 0 75	400 50	8 0	32 0 0 0	57 94	228 0 75 2	35 6	140 0 4 8	0 0	0 0 0 0	..	++	26 2 26 2	Not done Not done	Pneu. Type III Pneu. Type III	Pneumoc. (Type III) meningitis; septicemia; otitis media; broncho- pneu. and endocarditis.
16	III	0	+++	R L	0 75 1 00	830 1,625	25 26	207 5 422 0	38 36	315 4 585 0	34 32	282 2 520 0	3 6	24 9 98 0	..	++	9 0 9 0	Not done Not done	No growth No growth	Subac. bact. endocarditis; rheu. heart dis.; infarcts of kidney, spleen and brain.
17	IV	+	0	R L	3 00 7 00	128 48	8 7	10 2 3 4	28 43	35 8 20 6	64 50	82 0 24 0	0 0	0 0 0 0	+	+	10 0 10 0	Not done Not done	No growth No growth	Chr. glom. nephritis; hypertensive heart dis.; ascites; hydrothorax.
18	V	+	+	R L	0 80 0 50	50 50	6 6	3 0 3 0	64 40	32 0 24 5	28 39	14 0 19 5	2 6	1 0 3 0	++	..	9 0 9 0	Not done Not done	No growth No growth	Hypertensive heart dis.; pulm. in- faret.; bilat. bronchopneu.; hy- drothorax; hydropericardium.
19	V	+	+	R L	3 00 2 00	90 190	6 16	5 4 30 4	32 66	28 8 125 4	58 18	52 2 34 2	4 0	3 6 0 0	++		10 0 10 0	Not done Not done	No growth No growth	Pemphigus; thrombosis, left renal vein; infaret, left adrenal.
20	V	+	+	R L	10 00 13 00	110 70	75 50	82 5 35 0	0 50	0 0 35 0	25 0	27 5 0 0	0 0	0 0 0 0	.	++	10 0 10 0	Not done Not done	No growth No growth	Chr. glom. nephritis; rheu. heart dis.; bilat. hydrothorax and ascites.
21	VI	+	++	R L	7 00 3 50	115 345	54 68	63 1 231 6	46 31	52 9 106 9	0 0	0 0 0 0	0 1	0 0 3 5	++	..	5 5 5 5	Not done Not done	No growth No growth	Ac. bact. endocarditis; lung absce- infarcts, spleen and kidneys; ade- necarc. of gall bladder.
22	VI	+	+++	R L	2 50 1 50	220 355	64 48	140 8 184 8	34 38	74 8 146 3	0 10	0 0 38 5	2 4	4 4 15 4	++	..	18 0 18 0	Not done Not done	Hem. strep. Hem. strep.	Hem. strep. septicaemia; phlebitis rt. saphen. vein; pulm. and embolic absce.; ac. fibrinous pleuritis; uru- teritis (rt.).
23	VI	+	+++	R L	4 00 1 50	315 110	48 48	151 0 53 0	20 30	63 0 33 0	32 22	101 0 24 0	0 0	0 0 0 0	++	.	39 4 39 4	Not done Not done	Hem. strep. Hem. strep.	Pemphigus; chr. fibrinous pleuritis (left); pyelonephritis; hemolytic strep. septicaemia.
24	VI	+	+++	R L	16 00 20 00	22800 24,700	96 91	21,888 0 23,218 0	4 6	912 0 1482 0	0 0	0 0 0 0	0 0	0 0 0 0		++	19 4 19 4	Not done Not done	Hem. strep. Hem. strep.	Perforated appendix; append. absce.; peritonitis; hem. strep. septicaemia; diabetes mellitus; ac. nephritis.
25	VI	+	+++	R L	6 00 6 00	722 922	51 69	368 0 636 0	30 17	216 6 156 7	17 12	123 0 111 0	2 2	14 4 18 3		++	7 5 7 5	Not done Not done	No growth No growth	Sub. bact. endocarditis.

Tissue specimens from both knees of 15 patients and one knee of 2 others were normal (see Table 2 and Figure 1). The tissue from the opposite knee joint of one of the latter cases (Case 17) was slightly abnormal, showing small collections of lymphocytes, plasma cells and macrophages in the synovial tissues. As can be seen from Table 2 and Chart 4—24 of the fluids obtained from these 32 joints had normal total nucleated cell counts. Two of the remaining 8 had counts of 185 and 190 and in no instance did the counts

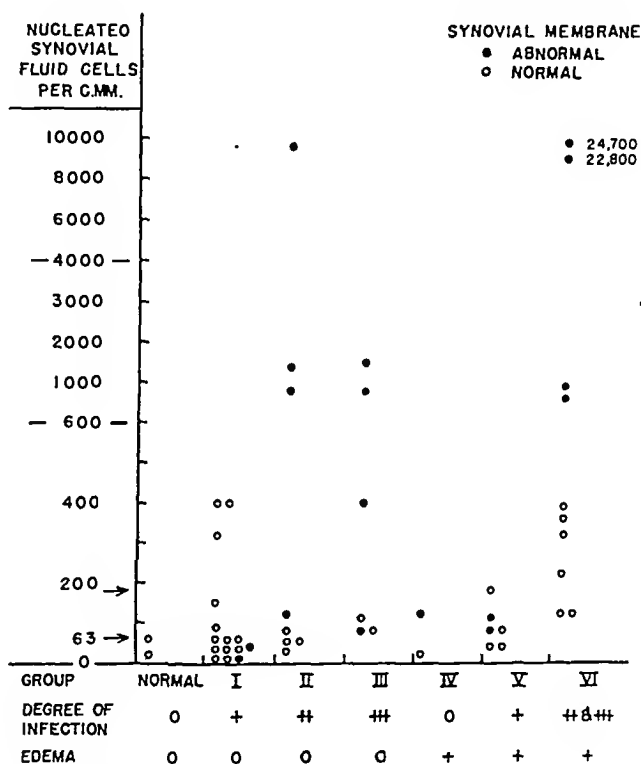


CHART 4.—Depicts the total synovial fluid nucleated cell counts of joints from which synovial tissue specimens were obtained. Normal human synovial fluids vary from 13 to 180, the average being 63 cells per c.mm. The synovial fluid and membrane abnormalities observed are readily apparent.

exceed 400. Twenty-one of these 32 fluids had normal absolute neutrophil counts (see Table 2 and Chart 5), while the remaining 11 varied from 24 to 234 neutrophils, the average being 109. Failure to remove adequate samples of synovial tissue may explain these slight discrepancies between fluid and tissue findings since often all portions are not equally involved by an inflammatory process. From these results it would appear that the synovial tissues may be expected to show little or no evidence of inflammation in those joints in which the total nucleated cell counts do not exceed 400.

Seventeen synovial tissue specimens showing microscopic evidence of inflammation were obtained from 9 (Cases 9, 12, 13, 15, 16, 17, 20, 24 and 25) individuals. The following table presents in concise form the chief histologic, clinical, and synovial fluid findings in these cases.

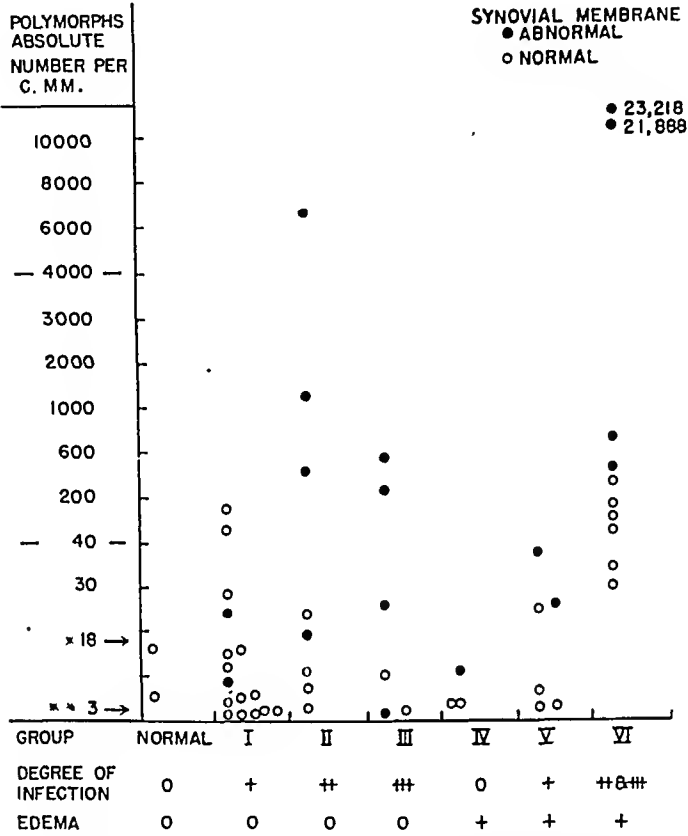


CHART 5.—Shows the number of neutrophils in synovial fluids from joints having abnormal synovial tissues. Only 3 of the synovial fluids from joints having abnormal synovial tissues had normal absolute neutrophil counts (0 to 18 per c.mm., the average being 3). It will be seen that in 11 instances the neutrophils were increased yet the synovial tissues from these same joints were normal.

TABLE 3.—CLINICAL, SYNOVIAL FLUID AND HISTOLOGIC FINDINGS IN THE CASES WITH ABNORMAL SYNOVIAL TISSUES.

Degree of synovial tissue inflammation.	No. of cases.	Grade of infection present.	Total nucleated cell counts.		Total neutrophils.	
			Normal.	Increased.	Normal.	Increased.
Minimal	5	1—none	5	0	2	3
		4—minimal				
Moderate	6	1—moderate	2	4	2	4
		5—severe				
Severe	6	3—moderate	0	6	0	6

Five specimens from Cases 9, 17 and 20 showed minimal inflammatory changes, consisting of small scattered perivascular accumulations of lymphocytes and plasma cells as illustrated in Figure 2. Mononuclears and neutrophils were present in small numbers.

Tables 2 and 3 reveal that such slight perivascular accumulations may be accompanied by an increase in the synovial fluid neutrophils even though the total cell counts are normal. Very slight increases in the size and number of synovial villi were present in these sections.

Six specimens obtained from cases of moderate and severe infection (Cases 12 [left knee], 13, 15 and 25 [left knee]) showed moderate inflammatory changes. Increased numbers of neutrophils, more evenly distributed than the other types of cells, were most frequent upon or within the synovial lining tissues. In addition, all types of inflammatory cells, diffusely scattered, and with less tendency to accumulate perivascularly, were present. As can be seen from



FIG. 2.—Minimal inflammatory changes seen in the synovial tissues from the right knee of Case 9 (Group II, Table 2). (Orig. mag. $\times 290$.) Here, the small focal areas of lymphocytic infiltration are readily seen. These focal lesions presumably accounted for the slight cytologic changes observed in the fluid obtained from this joint (50 nucleated cells of which 25 were neutrophils). (Celloidin section stained with hematoxylin-eosin.)

Tables 2 and 3, two of the synovial fluids in this group had both normal total nucleated and neutrophil counts. The synovial tissues from both knees of Case 15 showed the same degree of inflammatory change, yet the fluid from only the right was abnormal.

Six other examples from cases exhibiting moderate or severe infection (Cases 12 [right knee], 16, 24 and 25 [right knee]) showed extensive inflammatory changes. The tissue specimens obtained from Case 24, dying with severe infection (perforated appendix, appendiceal abscess and hemolytic streptococcus septicemia), exhibited marked acute inflammatory reaction characterized by widespread infiltration of the synovial lining and subsynovial tissues (see Fig. 3). Neutrophils predominated but mononuclears and

lymphocytes were present. Numerous bacteria consistent with streptococci were seen. The synovial fluid nucleated cell counts in these two instances were 22,800 and 24,700 per c.mm., 96 and 94% of which were neutrophils.

The four synovial tissue specimens removed from both knees of Case 16 and from the right knees of Cases 12 and 25 showed, in addition to slight diffuse and focal perivascular cell infiltration (Fig. 4), one or more sharply defined acute inflammatory lesions (Figs. 5 and 6), with marked infiltrations of neutrophils and mononuclears, fibrin deposition, and tissue necrosis. In 2 cases thrombosis

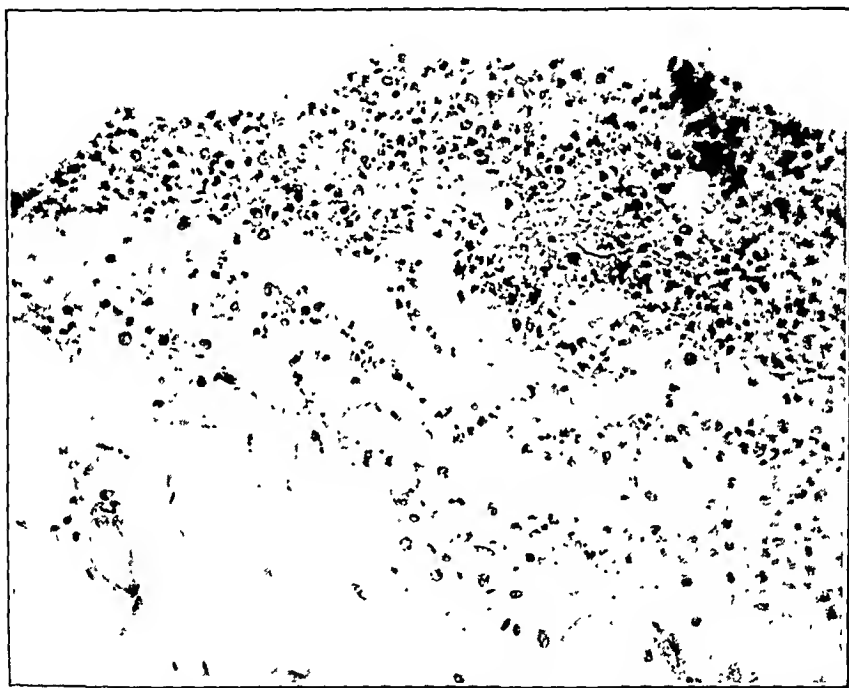


FIG. 3.—Heavy infiltration of the synovial lining and subsynovial tissues with neutrophils. (Orig. mag. $\times 290$.) A similar degree of acute inflammation was observed in the opposite joint. The total nucleated cell counts were 22,800 and 24,700 with 96% and 94% neutrophils, respectively (Case 24, Group VI).

of arterioles was observed. One of these lesions was perivascular and deep in the subsynovial tissues (Fig. 5), the others were in the synovial lining and the adjacent subsynovial tissue (Fig. 6). These lesions were probably embolic in nature, although no microorganisms were seen. The nucleated cell counts on the fluids from these last 4 joints varied from 830 to 1625; the absolute number of neutrophils ranged from 207 to 422. Microscopic edema was seen in the tissues from Cases 24 and 25.

It is interesting that the tissues from the right knee of Case 12 showed extensive inflammatory changes, whereas the specimen from the left knee showed only moderate change. The fluid from the

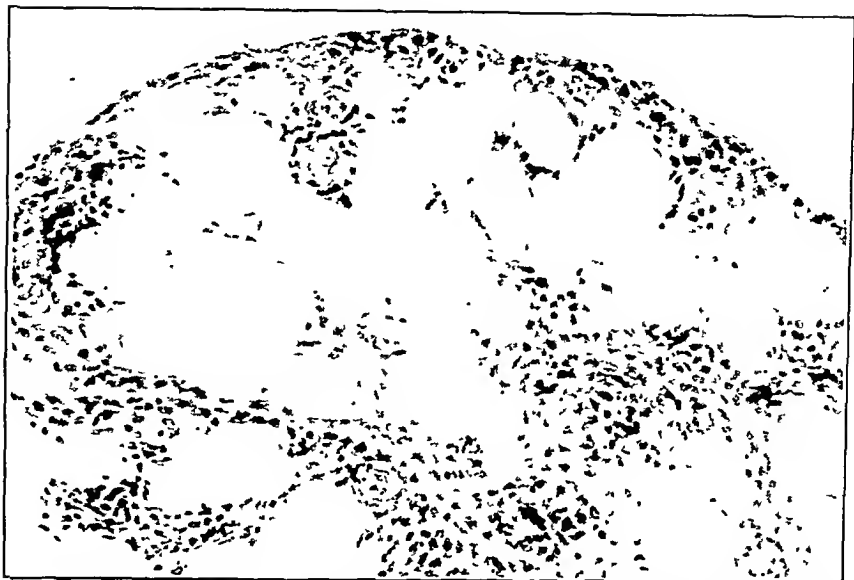


FIG. 4.—The synovial membrane over the infrapatellar fat pad of the right knee joint, showing numerous macrophages and neutrophils in perivascular areas and the synovial lining tissue. (Orig. mag. $\times 275$.) This patient, dying of subacute bacterial endocarditis had embolic lesions in various organs. Several inflammatory lesions like the one shown in Figure 5 were observed near large arterioles deep in the subsynovial tissues (Case 16, Group III, Table 2). (Celloidin section, hematoxylin-eosin stain.)

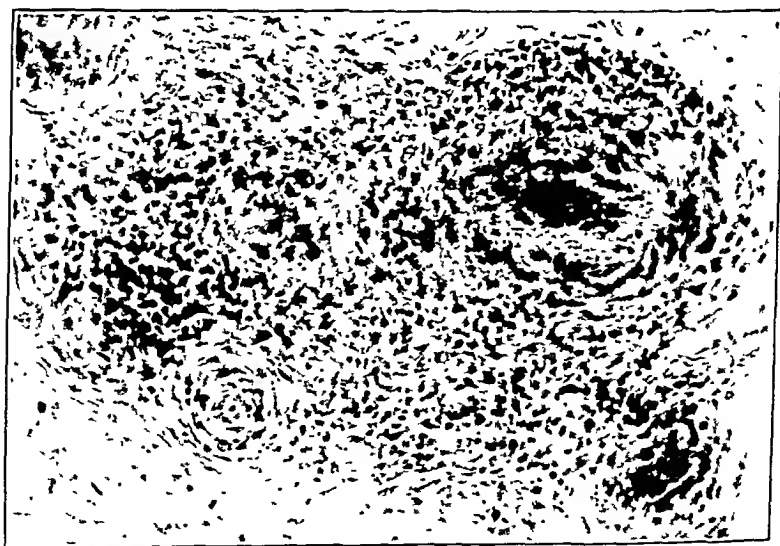


FIG. 5.—Another portion of the synovial membrane shown in Figure 4. This acute inflammatory lesion encircled a thrombosed arteriole. (Orig. mag. $\times 270$.)

right knee had total nucleated and absolute neutrophil counts of 920 and 405 respectively, while the counts of the left were normal. Similar findings were observed in Case 25, where, however, the fluid from the knee betraying the more extensive inflammatory changes showed the less marked cytologic abnormalities.



FIG. 6.—Sharply circumscribed acute inflammatory lesion in the synovial lining and subsynovial tissues from another patient dying of subacute bacterial endocarditis. (Orig. mag. $\times 275$.) The remaining portions of the synovial membranes removed from the two knee joints revealed only slight perivascular infiltration in the subsynovial tissues. Synovial fluid studies revealed an increase in total number of nucleated cells and also in the percentage of neutrophils. (See Case 25, Group VI, Table 2.)

Discussion. From the data presented, it is apparent that in the presence of local and generalized edema the amount of synovial fluid contained in a joint may be increased. The more marked the edema, whatever its cause, the greater is the synovial fluid content. This finding suggests that such increased formation of synovial fluid occurs where there exists a quantitative imbalance of the normal factors controlling the formation and absorption of interstitial fluid,⁵ namely, the colloidal osmotic pressure of the plasma, capillary and tissue pressures and capillary permeability. Synovial fluid specimens from edematous patients were paler and contained fewer cells than the normal. The total solids, viscosity, protein and mucin content of such fluids were lower than normal,⁹ signifying that the increased amount of synovial fluid was due to an increased

transudation of plasma water, low in protein content. These results are consistent with our previous contention^{2,8} that synovial fluid is a dialysate of plasma water containing mucin, which is added as the plasma water diffuses through the synovial tissues into the joint from the underlying blood-vessels. The evidence to date ^{2,8} is in keeping with the concept that mucin is formed by the functionally specialized mesenchymal tissues surrounding the joint cavity. Finding a lowered synovial fluid mucin content as a result of increased transudation into the joint implies that the rate of formation of mucin under such conditions is not so accelerated as the rate of transudation of water.

In other instances, the increased synovial fluid contents were the result of inflammatory exudation. In still others, both transudation and exudation seemed to participate, and it was impossible to ascribe the exact rôle.

From the results of the present study, it is apparent that the synovial fluid cytology is frequently altered in patients dying with infection. The synovial fluid cytologic abnormalities found in such cases are increased total nucleated cell and absolute neutrophil counts. Again it was found that elevation of the white cell count in the blood-stream is not, as such, reflected in the synovial fluid. The synovial fluid of patients dying with mild infections, of the type herein described, may show an increase in the absolute neutrophil count as the only evidence of existing synovial tissue inflammation. The fluid of an occasional patient with absent or only minimal clinical signs of infection evinced cytologic changes of inflammation in greater degree than would have been expected from the clinical observations. Since terminal septicemias occur frequently in moribund patients, it is not surprising to find such exceptions.^{4,6,7,11}

The interpretation of the significance of the synovial fluid abnormalities was facilitated greatly by examination of tissue specimens from the same joints. Occasionally the synovial tissues showed inflammatory changes although the corresponding synovial fluid cytology was normal. In such instances, the inflammatory focus was situated deep in the subsynovial tissues, suggesting that synovial fluid cytologic alterations resulting from infection are dependent not only upon the severity of the lesion but also on its proximity to the articular cavity. Absence of inflammatory changes in the synovial tissue specimens from joints exhibiting marked cytologic changes probably represents failure on our part to obtain an adequate sample of synovial tissue. As can be seen from Charts 4 and 5, an increase in the absolute neutrophil count is apparently a more sensitive index of inflammation of the articular tissues than is an increase in the total nucleated cell count. A total cell count of more than 400 probably indicates the presence of recognizable inflammation of the articular tissues. Such information should be of aid in the interpretation of pathologic joint effusions and allow

one to predict the extent and severity of the synovial tissue inflammatory lesion.

The severest synovial tissue inflammatory reactions and the most marked cytologic abnormalities were observed in patients dying with proved septicemias. In such cases, microscopic examination of the synovial tissues revealed occasional miliary abscesses containing organisms or inflammatory changes in and about thrombosed blood-vessels. Such inflammatory reactions serve as evidence that synovial membrane inflammation is the result of blood-borne infections.

In most cases the inflammatory changes in the subsynovial tissues were minimal and some distance from the joint cavity. Many of these lesions would probably have resolved completely in a relatively short period of time had the patients lived. This type of synovial tissue reaction would explain the transient aches and pains that occur during the course of acute infectious diseases with associated temporary bacteremia. Indeed, it is surprising that joint infections are not encountered more frequently under such circumstances, a fact which suggests that the tissues surrounding the joint possess high resistance to infection. The occurrence and degree of joint infection appear to depend more upon the adequacy of the normal defense mechanisms in the synovial tissues and the severity of the infection than the type of infective organism. The most marked joint reactions observed in this study would probably have been recognized as specific infectious or septic arthritis had the patients not been moribund.

Conclusions. From a study of 156 postmortem synovial fluids and 49 synovial tissue specimens obtained from individuals dying with varying degrees of infection and edema, the following conclusions can be drawn:

1. The amount of synovial fluid in the knee joints of individuals with peripheral edema is usually increased.
2. The synovial fluid obtained from the joints of edematous patients contains fewer nucleated cells than does normal fluid and its total solids, viscosity, protein and mucin contents are reduced.
3. The total nucleated cell counts and the absolute number of neutrophils in synovial fluid specimens obtained from patients dying with varying degrees of infection are frequently increased. The most marked cytologic abnormalities are observed in patients dying with severe infections and associated septicemias.
4. An increase in the absolute number of neutrophils is a more reliable indication of the existence of synovial tissue inflammation than are increased total nucleated cell counts or random biopsies.
5. The synovial fluid abnormalities resulting from synovial tissue infections vary with the severity of the synovial lesion and its proximity to the joint space.
6. The results of the present study suggest that the joint aches

and pains occurring in various infectious diseases may be the result of synovial tissue inflammatory changes caused by blood-borne infections. The majority of such inflammatory lesions are presumably mild in nature and therefore resolve readily. The marked synovial tissue reactions observed in patients dying with septicemia are of the type observed in early cases of specific infectious or septic arthritis.

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STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT.*

I. THE INTAKE OF THIAMINE AND ITS RELATION TO OTHER DIETARY CONSTITUENTS IN FOOD SELECTED BY THE NORMAL SUBJECT.

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THE purpose of this study was to determine the actual thiamine intake of a group of normal persons who were permitted to select from an adequate available diet the amount and type of food which they desired. Such information, it was thought, would indicate to what extent the food chosen under such circumstances contains the amount of the vitamin regarded as necessary to meet bodily needs, to what extent individual preference determines the amount ingested and to what extent the amount normally selected by the individual varies from day to day.

* Under this title will appear serially in this Journal several articles from the Thompson Vitamin Clinic of the Philadelphia General Hospital. This Clinic, sponsored by the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, University of Pennsylvania Hospital, and by the Philadelphia General Hospital, is generously supported by Mrs. Arthur W. Thompson. The work is being supervised by an advisory committee, consisting of Drs. Truman G. Schnabel, William G. Turnbull, J. H. Clark, Walter G. Karr, George Wilson and T. Grier Miller, and the chemical studies are being carried out under the supervision of Dr. John G. Reinhold, Chief of the Division of Biochemistry of the Philadelphia General Hospital. Miss L. M. Johnson and Miss Elizabeth Miller, respectively Directress of Nurses and Dietitian of the Philadelphia General Hospital, have coöperated. The vitamin preparations, except when otherwise noted, have been supplied by Merek & Co.

It was found in a selected group that the thiamine intake exceeded the theoretical requirement in most instances, but varied greatly among individuals and in the same persons from day to day; that the consumption of protein and of thiamine were directly related, and that some correlation existed between the intake of fat and of thiamine, whereas no correlation was demonstrable between the thiamine, on the one hand, and the total caloric or carbohydrate intake, on the other.

Methods. Seven women, essentially normal and resident in the Vitamin Ward of the Philadelphia General Hospital, were permitted to select from an adequate diet the type and quantity of food which they desired for periods of from 15 to 39 days. All of the food was carefully weighed. The total daily intake of thiamine was calculated from the Cowgill tables,⁵ and also from figures compiled by Williams and Spies.²⁶ Corroboration of the calculated values was obtained by chemical analysis of daily diets on 3 occasions, using a modification of the thiochrome method of Hennessy and Cerecedo¹⁵ and Hennessy¹⁴ as described elsewhere.⁹ The protein, fat, carbohydrate and caloric values were obtained from standard tables.³ The theoretical thiamine requirement for each individual was calculated in micrograms of thiamine according to the Cowgill formula,⁵ $\frac{\text{Vitamin B}_1}{\text{Calories}} =$

$0.0000284 \text{ W gm.} \times 0.166$, using the average caloric intake and average body weight during the time of observation. The subjects were weighed daily under standard conditions and were observed closely for the development of symptoms and abnormal physical signs. The fluid intake was maintained at 1500 cc., and 24-hour collections of urine were obtained. Analyses for the thiamine in the urine were made by the same method as for the food and will be reported in another communication.⁹

TABLE 1.—THIAMINE REQUIREMENTS AND INTAKE ON SELF-SELECTED DIET.

Subject.	Length of observation (days.)	Age (years).	Average body weight* (kg.).	Theoretical requirement for thiamine (μg.).	Av. daily intake of thiamine (μg.).
1	30	64	57 5	524	663
2	30	65	59 0	503	691
3	30	38	78 0	715	760
4	30	52	65 0	610	784
5	30	52	43 0	380	817
6	15	36	71 7	646	842
7	39	45	54 3	574	973
Average	25	50	60 0	565	789

* Subjects 3 and 6 lost 1.3 and 0.8 kg. respectively; the others either maintained or gained weight. The group as a whole gained 0.5 kg.

Results. 1. *Thiamine Intake in Relation to Theoretical Requirement.* The average daily intake of thiamine by the entire group was 789 μg., while the average theoretical requirement was 565 μg. (Table 1). The intake thus exceeded the requirement by 40% in the group as a whole. The individual variation in this respect, however, was great. For example, Subject 3 exceeded her need for the vitamin by only 6% (Chart 1), and for approximately one-half the period of observation failed to consume the required

amount. Likewise, Subject 1, whose average intake was 26% above her requirement, failed to obtain an adequate amount for one-quarter of the period. At the other extreme, Subject 5 exceeded her theoretical requirement by 115% and never failed to consume less than 40% above that amount. Thus it is apparent that individual food habits are an important determining factor in the margin of safety maintained with respect to thiamine intake.

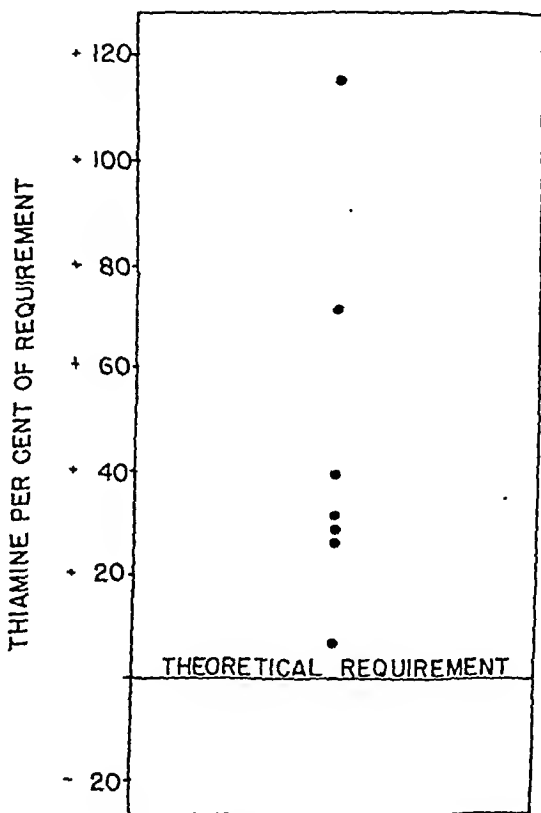


CHART 1.—Average daily intake of thiamine as per cent of requirement for each member of the group.

The subjects with a minimal intake showed clinical evidence of a thiamine deficiency during the time that the food selected by them was below their requirement. Thus Subject 1, who was known to have taken a borderline diet prior to admission to the hospital, complained of easy fatigability, heartburn, epigastric distress and pains in the extremities and showed tenderness to pressure over her peripheral nerves and edema. These symptoms and signs regressed when the intake of thiamine was adequate. Subject 3, whose inadequate selection of foods was of shorter duration, developed the phenomena of deficiency later than Sub-

ject 1. These observations, together with the fact that at no time did the other 5 subjects show any evidence of deficiency tend to confirm the accuracy of the calculations of theoretical requirement.

TABLE 2.—FOOD SELECTED BY SUBJECTS 1 AND 5, OCTOBER 6, 1940.

Article.	Subject 1.						Subject 5.					
	Wt. (gm.).	Prot. (gm.).	Fat (gm.).	Carb. (gm.).	Cal.	Thia- mine (μ g.).	Wt. (gm.).	Prot. (gm.).	Fat (gm.).	Carb. (gm.).	Cal.	Thia- mine (μ g.).
Breakfast:												
Egg	50	7	5	..	75	48	50	7	5	..	75	48
Cream of Wheat .	166	3	..	24	116	16						
Bread	11	1	..	6	29	5	33	3	..	17	86	13
Milk	150	5	6	8	105	81
Lunch:												
Ham (boiled) . .	99	18	5	..	149	197	99	18	5	..	149	197
Potatoes (boiled).	100	3	..	25	110	67	100	3	..	25	110	67
Peas	60	2	..	6	30	78	60	2	..	6	30	78
Bread	22	2	..	11	57	9
Butter	12	..	10	..	96	16	12	..	10	..	96	16
Custard	75	3	4	9	83	48	75	3	4	9	83	48
Milk	150	5	6	8	105	81
Supper:												
Pea soup	150	7	2	15	135	81	75	4	1	8	68	41
Frankfurter	120	23	22	1	312	334
Bread	22	2	..	11	57	9	44	4	1	23	114	18
Butter	6	..	5	..	48	8	12	..	10	..	96	16
Milk	180	6	7	9	126	97
Sugar (total) . .	74	74	289	..	2	2	8	
Total	46	31	170	1217	573	..	85	77	127	1620	1144

No correlation between the individual theoretical requirement for thiamine and its intake was observed. For example, Subject 5 had the lowest requirement, but her average intake was greater than that of any but two of the group (Table 1). This is further strikingly demonstrated by the daily records of thiamine intake by Subjects 1 and 5 (Chart 2). It will be noted that the individual with the lower requirement consistently selected food of greater thiamine content. For example, on the first day of observation Subject 1, whose requirement was 524 μ g., obtained 573 μ g. from the available diet, while Subject 5, whose requirement was 380 μ g., obtained 1144 μ g. Analysis of the food intake on that day (Table 2) shows that, whereas the higher intake of thiamine was associated with a greater total number of calories, the difference could not be explained entirely by this fact, but was the result of a greater preference on the part of this subject for foods rich in thiamine. Thus it would appear that food habits rather than needs determined the level of thiamine intake in this group.

2. *Daily Variation in Thiamine Intake.* In addition to the wide divergence in intake between the several members of the group, a large variation occurred from day to day in each individual. Two factors appeared to be responsible for this. Firstly, differences in

the thiamine content of the available food produced fluctuations in intake. For example, on a given day when pork, which is rich in the vitamin, was included in the diet, a sharp rise in the thiamine intake was observable for each member of the group. Secondly, individual food habits modified the intake, depending upon the individual's like or dislike for certain articles of the diet. The magnitude of this individual variation was greatest in Subject 5, whose intake on one day exceeded the mean by 72% and on another fell below it by 60%. At the other extreme was Subject 1 who never departed from the mean intake by more than 50%. It is scarcely surprising therefore to find in the literature^{2,4,18,21,24} evidence of wide fluctuations in thiamine output among normal persons. Such figures are without great significance unless they are considered in relation to the thiamine intake which our observations prove fluctuate widely.

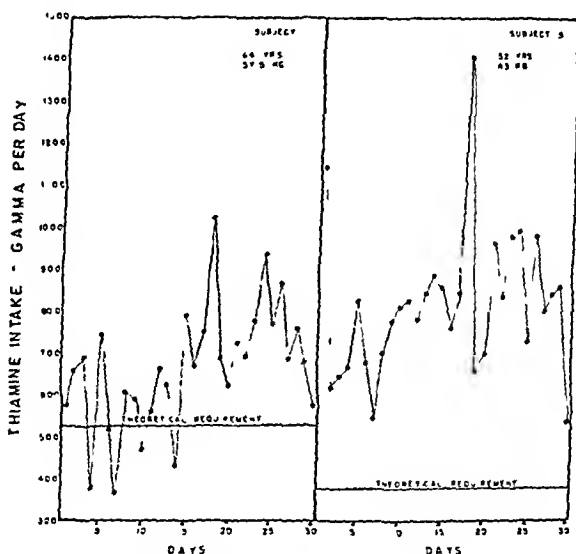


CHART 2.—Daily intake of thiamine in relation to requirement for Subjects 1 and 5.

3. *The Relation of Thiamine Intake to That of Other Dietary Constituents.* A linear relationship existed between the daily intake of protein and of thiamine (Chart 3). This relationship, found to be statistically valid, existed for the group as a whole as well as for each individual member.* This was not, as might at first appear,

* We are indebted to Dr. E. D. Burdick for making the statistical calculations to prove the validity of this relationship. The coefficient of correlation was 0.728 calculated by the formula:

$$\frac{N\sum XY - (\sum X)(\sum Y)}{\sqrt{[N\sum X^2 - (\sum X)^2][N\sum Y^2 - (\sum Y)^2]}}$$

The variance around the regression line was 19.11 as calculated by the formula:

$$\sqrt{\frac{\sum Y^2}{N} - \left(\frac{\sum Y}{N}\right)^2}$$

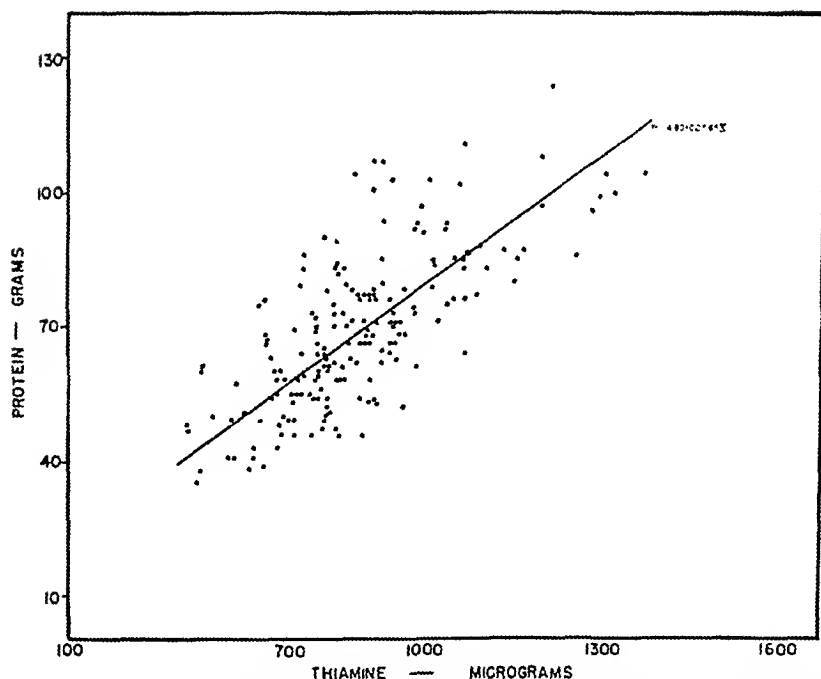


CHART 3.—Protein in relation to thiamine in food selected by the group. Each point in the diagram represents the total protein and thiamine consumed by each individual during each day.

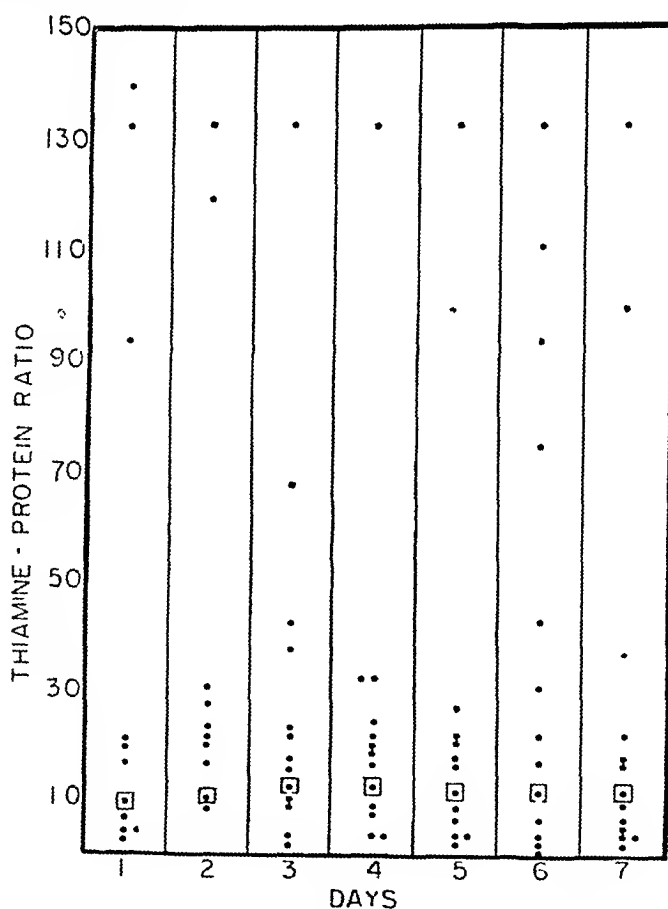


CHART 4.—The thiamine-protein ratio of the different foods and of the total food consumed by Subject 6 for each of 7 days. The enclosed points indicate the thiamine-protein ratio of the total food consumed each day.

simply an expression of the fact that protein foods by and large are rich in thiamine. Analysis of foods making up the diet shows that some foods, such as noodles, rice and cheese, provide a large amount of protein but a small amount of thiamine. Conversely, milk, apricots, pork, potatoes, oatmeal, raw cabbage, liver and Ralston cereal fortified with wheat germ, appearing often in the diet, are proportionally richer in thiamine than in protein. Thus great variability in the thiamine-protein ratio existed for individual foods, while it was constant for the total food consumption on each day (Chart 4). Hence a linear relationship between thiamine and protein need not necessarily have existed. When, however, the subject was given a free choice of protein foods, a mixture was

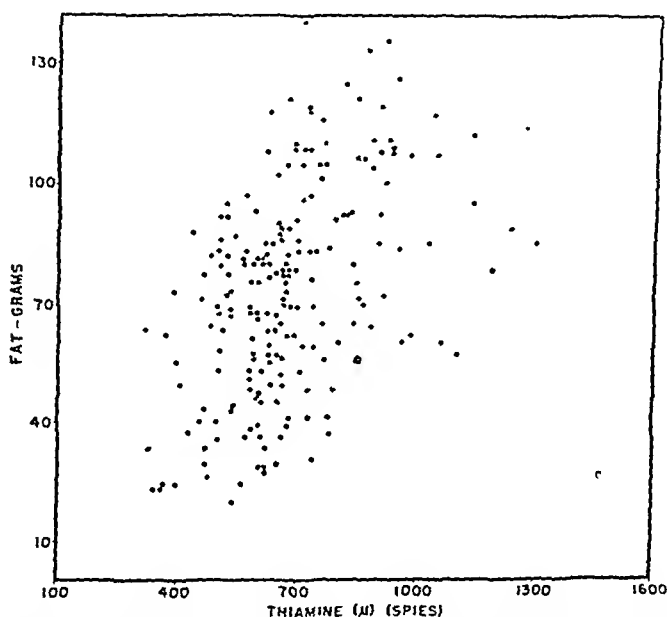


CHART 5.—Fat in relation to thiamine in food selected by the group. The values for thiamine used in preparation of this figure were those given by Williams and Spies.²⁶ No thiamine value for fat is included in these values and therefore the positive correlation between fat and thiamine here demonstrated is independent of the relationship inherent in the Cowgill figures where thiamine values are assigned to fat on the basis of the known thiamine-sparing action of fat.

selected which provided a fairly constant ratio of protein to thiamine and resulted in the linear relationship described.* Whether this relationship obtains in a deficiency-producing diet is a subject that deserves separate study.

* It is probable, also, that a similar relationship existed between protein and other members of the B complex in this diet. However, figures for the concentration of these substances in foods are not sufficiently complete to permit calculation of the dietary content.

A positive correlation, though less definite than in the case of protein, was observed between the consumption of fat and of thiamine (Chart 5). No such correlation, however, was observed

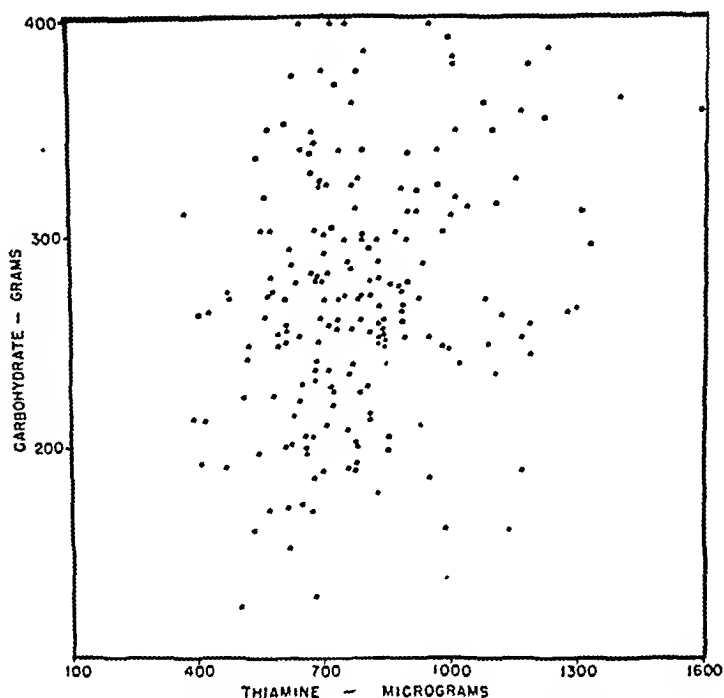


CHART 6.—Carbohydrate in relation to thiamine in food selected by the group.

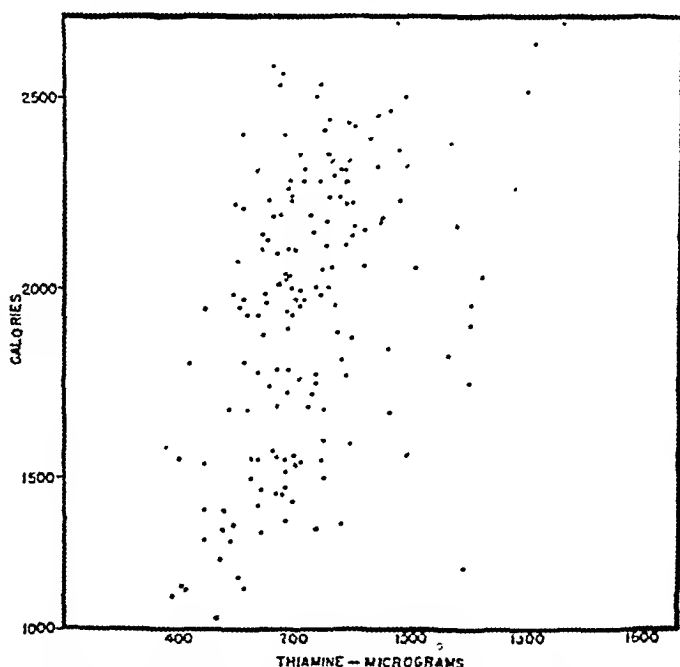


CHART 7.—Caloric intake in relation to thiamine in food selected by the group.

between daily carbohydrate and thiamine (Chart 6) or between total daily caloric and thiamine intake (Chart 7).

Discussion. The widely different amount of thiamine obtained from the same available food by these subjects demonstrates clearly that the adequacy of the vitamin intake cannot be determined alone from a knowledge of its content in the available food. That a vitamin deficiency may develop even in the presence of an adequate food supply and that this deficiency may be determined primarily by individual food habits are demonstrated by the failure, on frequent occasions, of two of the subjects to meet their needs for thiamine while other members of the group, living under identical conditions, obtained amounts which greatly exceeded their requirement. This observation may explain also the seemingly puzzling fact that deficiency disease often afflicts only one or two members of a household in which the remainder are healthy.

The food consumed by these subjects was inexpensive, costing approximately \$2.80 per week per person as purchased from the usual retail sources. That it supplied thiamine in more than an adequate amount for any normal person is demonstrated by the fact that one subject obtained from it an average of 973 μ g. which is an amount sufficient to meet the theoretical requirement of an individual weighing 181 pounds.⁵ Stiebeling and Phipard²³ have recently reported that a weekly expenditure of \$3.50 to \$3.12 for food in the North Atlantic States resulted in poor diets in 53% of the cases while others^{16,22} have likewise suggested that the diet of the average American in the low income group is borderline with respect to thiamine. That such observations based only on several surveys of available food, are at variance with our objective idea on individual subjects tends further to emphasize the fact that, except in grossly limited diets, the adequacy or inadequacy of a given diet can be determined only by a careful analysis of food intake by the individual in relation to his requirement.

Whether the quantitative relationship between protein and thiamine which existed in the food consumed by these normal subjects is an essential of a normal diet requires further study. That such a quantitative relationship between dietary factors may be of importance has recently been demonstrated in the case of cystine and choline.^{11a,b,c,d} There is evidence also that the ability to utilize protein is dependent on the presence in the diet of a proportionate amount of the vitamin B complex. Thus in 1924 Hartwell^{12a} and later Reader and Drummond²⁰ and others^{6, 12b, 13} found that when the protein was increased out of proportion to the B complex in the diets of young rats growth was curtailed. The component of the vitamin B complex concerned in this response has not been identified.^{10,19} In humans, observations bearing on the relationship of the B vitamins to nitrogen metabolism are few. Elsom, Dickey and Chornock,⁸ studying the absorption of nitrogen

in subjects with ulcerative colitis, could find no correlation between clinical evidence of vitamin deficiency and decreased nitrogen absorption. On the other hand, one of us,^{7a} studying a human subject maintained under constant conditions of experimental B complex deficiency, observed a positive nitrogen balance coincident with gain in body weight following addition of yeast to the diet. On another occasion^{7b} urinary nitrogen excretion was found decreased during B complex deficiency.

The quantitative relationship between fat and thiamine in these diets recalls the work of Whipple and Church²⁵ and more recently of McHenry and Gavin¹⁷ and others¹ who have suggested that thiamine is concerned in the metabolism of fat.

Summary. 1. Seven subjects, maintained under controlled conditions, were given access to an adequate diet from which they selected the type and quantity of food desired.

2. The average daily intake of thiamine exceeded the theoretical requirement for that vitamin by 40% for the group as a whole, but the individual intake ranged from 6 to 115% above the requirement. In addition to a wide divergence of thiamine intake among the several members of the group, a large variation occurred from day to day in the same individual.

3. Individual food habits appeared to be an important determining factor in the margin of safety maintained with respect to the thiamine in the diet.

4. A linear relationship existed between the daily intake of protein and of thiamine, both for the group as a whole and for each individual. This relationship resulted from the selection of foods of both high and low protein content in such a proportion as to produce a fairly constant ratio, but one that did not pertain to the individual foods consumed.

5. A positive correlation, of lesser degree than that between the protein and the thiamine, was observed between the fat and the thiamine content of the diet. No correlation existed between the carbohydrate and the thiamine or between the calorie intake and the thiamine of the diet.

We wish to express our appreciation of the faithful nursing care rendered by Misses Ruth Conrad, Ruth Kruger, Elizabeth Villella and Ruth Jett; of the assistance with the diets given by Miss Alice Knudsen, and of the secretarial assistance provided by Miss Ellen Jones.

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STUDIES OF THE B VITAMINS IN THE HUMAN SUBJECT.

II. URINARY EXCRETION OF INGESTED THIAMINE IN PATIENTS WITH CHRONIC HEPATIC DISEASE.*

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THE influence of hepatic disease on the excretion of thiamine in the urine has not been definitely ascertained. The concept of its phosphorylation in the liver, as based on the studies of Ochoa and Peters⁷ and of Westenbrink and Goudsmit,^{11a} has led to the opinion that there should occur a greater urinary excretion of the vitamin in liver disease, and this idea has been supported by Borson,¹ who noted an unusually high excretion in 3 patients with hepatic cirrhosis following the administration of daily test doses. On the contrary, Robinson, Melnick and Field⁸ found low values for its urinary excretion in 3 patients with hepatic disease following the administration of a single test dose. They attributed this to a previous sub-optimal intake in their patients. In an attempt to obtain more data on the problem, we have made simultaneous observations on subjects with and without hepatic disease while on a basal diet and while on such a diet supplemented with small additional amounts of thiamine chloride orally administered.

* Presented before the American Federation of Societies for Clinical Research, May 5, 1941, at Atlantic City, N. J.

Procedure. Three of the 6 female subjects in the vitamin ward of the Philadelphia General Hospital, who were used for this study, had clinical and laboratory* evidence of chronic hepatic disease; the remaining 3 had no such disease and were used as controls. All had satisfactory renal function as judged by the standard urea clearance test, and none had any signs of a B-complex deficiency.

The thiamine requirement for each subject was calculated from Cowgill's² formula, and this amount together with an adequate number of calories and the other essentials were included in a basal diet. After a preliminary observation period of about 2 weeks, during which they were allowed access to as much of the house diet as they wished, the subjects were placed on the basal diet for 16 to 37 days, and later it was supplemented with varying amounts of additional thiamine, to as much as 1000 μ g. daily. The total daily fluid intake was limited to 1500 cc., and 24-hour urine specimens were collected. The urine, as voided, was placed in individual bottles kept in a refrigerator, glacial acetic acid being added to prevent decomposition of the thiamine. The amount of thiamine in each 24-hour specimen was determined by a modification of the thiochrome method of Hennessy and Cerecedo⁵ to be described in another paper.³

Results. 1. *Excretion on the Basal Diet.* No significant difference was observed in the percentage of the thiamine excreted in the urine by the patients with hepatic disease and by the controls while on the basal diet, all 6 excreting 6.5 to 8.7% of the amount ingested (Table 1).

TABLE 1.—URINARY EXCRETION OF THIAMINE.

Case.	On basal diet.		On basal diet plus added thiamine.	
	Average daily thiamine intake (μ g.).	Average daily urinary excretion (%).	Average daily thiamine intake (μ g.).	Average daily urinary excretion (%).
1. Laennec's cirrhosis (F.R.)	715	8.7 (4.0-13.5)	1752	14.3 (3.3-27.2)
Control (A.T.)	527	6.5 (4.0-7.8)	1532	17.4 (7.5-26.0)
2. Banti's syndrome (A.H.)	652	8.2 (6.1-14.2)	1641	13.8 (10.0-16.5)
Control (M.H.)	422	8.2 (4.7-10.1)	1459	20.4 (14.8-25.2)
3. Banti's syndrome	651	7.2 (4.0-10.1)	1651	20.7 (18.8-22.0)
(Post-splenectomy) (S.L.)				
Control (J.Z.)	706	8.3 (4.3-11.9)	1655	26.5 (23.2-30.0)

Average total daily thiamine intake and percentage of this excreted in the urine while on basal diet and when such a diet was supplemented with 1000 μ g. of thiamine daily by mouth. Figures in parenthesis represent range of excretion.

2. *Excretion on the Basal Diet Supplemented with Thiamine.*

A. A patient with Laennec's cirrhosis and her control were given by mouth 1000 μ g. of thiamine chloride† daily in addition to the basal diet for a period of 14 days. The excretion of the patient with the liver damage rose less rapidly and to a lower level than did

* An elevated icteric index, retention of bromsulphalein and impairment of hippuric acid synthesis.

† Generously supplied by Merek & Co., Rahway, N. J.

that of the control. The average percentage excretion for the 14-day period was 17.4% for the control and 14.3% for the cirrhotic.

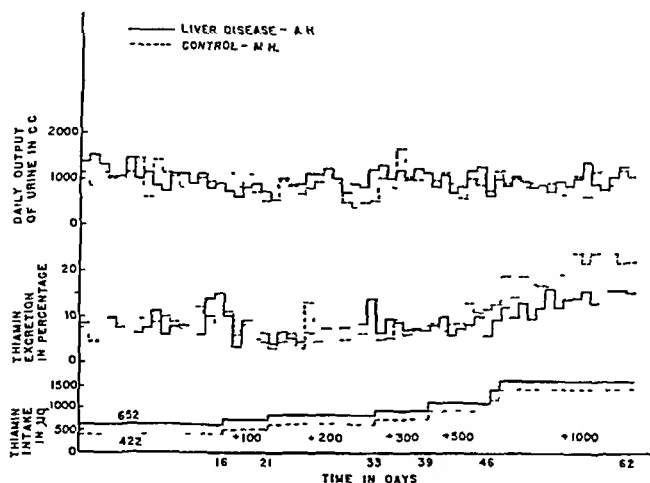


CHART 1.—Daily thiamine intake, urinary excretion and daily 24-hour urine volume output of a patient with Banti's syndrome and of her control.

B. To a patient with Banti's syndrome and to her control the supplements of thiamine were added in increments gradually increasing until 1000 μ g. were being administered daily. In this instance also the excretion of the patient with the damaged liver lagged behind and did not reach the height of the control. When 1000 μ g.

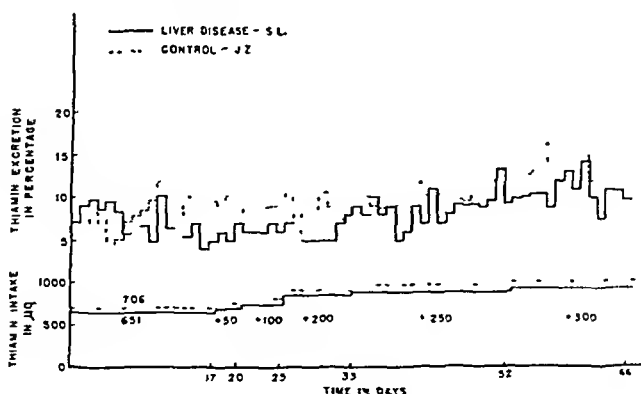


CHART 2.—Daily thiamine intake and urinary excretion of a patient with a post-splenectomy Banti's disease and of her control.

daily were being added, the patient with hepatic disease excreted an average of 13.8% of the ingested thiamine as compared to 20.4% for the control. Furthermore, the total volume of the urine excreted daily over the entire period bore no relationship to the percentage of the thiamine excreted (Chart 1).

C. To a patient with postsplenectomy Banti's syndrome and to her control the supplements were given in smaller increments in order to determine whether or not a slow increase in the thiamine intake would dispel the difference in excretion observed in the previous experiments. Though no lag in the excretion for the subject with liver disease occurred, the level of excretion was persistently lower than in the control. When each subject received a daily supplement of 1000 $\mu\text{g.}$, the patient with the damaged liver excreted on the average 20.7% of the ingested thiamine while the control excreted 26.5% (Chart 2, Table 1).

Comment. These data indicate that when supplements of thiamine, up to 1000 $\mu\text{g.}$ daily, were added to the basal diet the patients with hepatic disease excreted less than did the controls. Such observations are not in accord with the claim¹ that, because phosphorylation of thiamine occurs in the liver, the urinary excretion of ingested thiamine should be higher in the subjects whose livers are damaged. It must be admitted, however, that, providing its absorption in the intestinal tract is not impaired, the amount of thiamine phosphorylated may be determined by the type and extent of liver damage.

The following possibilities in explanation of the lessened excretion in our hepatic cases are suggested:

1. *Disturbed Renal Function.* That this was not the important factor in our subjects is indicated by the satisfactory urea clearance in each of them. Furthermore, daily determinations of the volume and the specific gravity of the urine showed no significant deviations.

2. *Previous State of Tissue Unsaturation.* The patients with liver disease received a B-complex preparation prior to their becoming the subjects for our study. Furthermore, while in the vitamin ward, they ingested from 600 to 1500 $\mu\text{g.}$ of thiamine contained in food per day for at least a month before receiving the supplements of thiamine and during that time the urinary excretion of thiamine was within normal range. Thus a previous state of unsaturation cannot be claimed as being responsible for the decreased level of excretion in the subjects with hepatic disease.

3. *Absorption from the Intestinal Tract.* An impairment of absorption from the intestinal tract must be seriously considered, since all 3 of the liver cases had clinical evidence of portal back pressure. Such a factor is known to impair the absorption of substances which are transferred across the intestinal wall by diffusion, and it has recently been shown by Stockholm *et al.*¹⁰ that, in rats, thiamine is so absorbed. Furthermore, using very high test doses of thiamine, Westenbrink and Goudsmit^{11b} and also Borson¹ observed that, following oral administration, unlike parenteral administration, the percentage of thiamine excreted in the urine varies inversely with the size of the dose administered. This unabsorbed thiamine appears in the feces, as has been demonstrated by Leong,⁶ Shultz *et al.*⁹ as well as in our clinic.⁴ Further studies using an intestinal intubation

technique which we have planned, are necessary to settle this matter finally.

Summary. On a basal diet no essential difference occurred in the percentage of ingested thiamine excreted in the urine of patients with hepatic disease and in that of control subjects. When such a basal diet was supplemented with thiamine, not over 1000 $\mu\text{g.}$, the patients with liver disease excreted less. The possibility is discussed that an impairment of intestinal absorption in our patients with hepatic disease, consequent upon portal back pressure, accounts for this difference.

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PROTEIN-BOUND IODINE IN BLOOD.

V. NATURALLY OCCURRING IODINE FRACTIONS AND THEIR CHEMICAL BEHAVIOR.*

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DURING the past two decades microchemical methods for the estimation of the small amounts of iodine that are found in the

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circulation have improved steadily, so that the values obtained by rather different procedures now corroborate one another. Although the absolute magnitude of these figures is still open to question, the reliability of the methods now available justifies a qualitative study of different iodine fractions in the blood. In previous studies from this laboratory the thyroidal activity of iodoproteins has been described.^{10a,b 12,16} It is the purpose of this communication to describe certain protein-bound iodine fractions which may be separated from human and animal blood.

In 1900 Gley and Bourcet⁶ studied the iodine present in amounts of dog plasma as large as 1 liter. They found an average value of 5 μ g. per 100 cc. and upon dialysis they were able to remove only a negligible portion of the total iodine. They concluded, therefore, that the naturally occurring iodine in the plasma is bound to protein. Since then, numerous other approaches to this problem have been made, of which it is possible to cite here only a few examples. A more detailed review has been published elsewhere.¹⁵ Bier and Roman² dialyzed ox serum for 10 days and were able by this procedure to remove only about one-fourth of the iodine present. Similarly, Leipert⁸ found that ultrafiltrates of horse serum yielded less than half of the iodine in the filtrate. More recently, Trevorrow²⁰ found that the major portion of the plasma iodine was precipitated with the plasma proteins either by heat coagulation with acetic acid¹ or by precipitation with zinc sulphate and sodium hydroxide.¹⁹ Although a great deal of work reported in the literature has to do with the use of organic solvents, *e. g.*, alcohol or acetone, to remove protein-bound iodine, it should be emphasized that this method has not been employed in the present observations because organic solvents yield variable results according to the details of the procedure followed. This problem has been discussed in detail elsewhere.¹⁵

General Methods. *Collection of Blood.* When fresh blood was drawn, extreme care was exercised to prevent contamination with iodine through the use of chemically clean, iodine-free glassware and blood anticoagulant (potassium oxalate or heparin).

Determination of Iodine. Two methods were used to determine total iodine in the different fractions. These were (a) the aeration procedure of Fashena and Trevorrow⁵ following oxidation with dichromate; and (b) the distillation method of Riggs and Man¹⁴ following oxidation with permanganate. The two series of values coincided so closely that no distinct difference could be discerned.

The data presented in this communication concern mainly the plasma; whole blood was avoided because the distribution ratio of "hormonal" iodine between the intra- and extra-corporeal protein components of whole blood is still disputed. Preliminary experiments with heat coagulation yielded results which are summarized in Table 1. The whole blood was laked and the protein components separated as follows: The plasma proteins were precipitated by heat at pH 5.3 and the hemoglobin by heat at pH 6.6; the iodine bound to each protein fraction was then determined. The separated plasma was analyzed as described later. From the hematocrit

values given in Table 1, the protein-bound iodine content of the erythrocytes may be calculated if desired. The problem of the natural iodine content of red cells, however, is still under discussion.^{7,13} Nevertheless the results in the table demonstrate that over a considerable range of physiological thyroid activity the use of plasma gives a wider spread in iodine values and thus affords a greater sensitivity of the chemical method. These data are not presented, therefore, as the final solution to the question of intracorpuseular iodine. Rather, they constitute a valid reason for avoiding the use of whole blood when the present technique is employed.

TABLE 1.—PROTEIN-BOUND "P" IODINE IN WHOLE BLOOD AND PLASMA.

Case No.	Sex.	Age.	B.M.R.	Hemato- crit.	Whole blood µg. per 100 cc.	Plasma, µg. per 100 cc.	Ratio plasma/ whole blood.	
<i>Myxedema.</i>								
4	.	M	42	-32	41.6	3	3	0.9
3	.	F	41	-37	35.4	3	2	0.6
1	.	F	44	-45	33.0	2	2	0.9
7	.	F	73	-42	2	
6	.	F	55	-18	1	
11	.	F	62	-21	2	
Average			-33	..	3	2	0.8	
<i>Euthyroidism.</i>								
109	.	M	19	-9	40.1	5	6	1.1
82	.	F	31	+21?	44.9	6	5	0.9
99	.	F	41	+36	49.8	6	6	1.0
101	.	F	25	0	40.4	6	5	0.9
107	.	M	52	-3	48.6	5	5	1.0
Average			+2	..	6	5	1.0	
<i>Hyperthyroidism</i>								
41	.	F	59	+36	43.6	9	11	1.3
39	.	M	19	+45	42.5	9	12	1.3
34	.	F	31	+50	42.8	9	11	1.3
A.M.*	.	F	47	+61	39.0	8	13	1.7
Average			+48	..	9	12	1.4	

* B.C.H. No. 981559.

IODINE DISTRIBUTION IN PLASMA: *Separation of Inorganic ("I") from Protein-bound ("P") Iodine.* Plasma was separated by centrifugation shortly after the blood was drawn and treated as follows:

One volume of plasma (usually 10 cc.) was added dropwise with constant stirring to a 50 cc. centrifuge tube containing 3 volumes of 0.02 normal acetic acid. The tube was placed in a water bath which was brought to boiling within a period of 10 minutes, and the mixture was stirred constantly throughout the process of coagulation. By this time the supernatant liquor appeared water clear and the precipitate showed definite flocculation. The final pH was 5.3. After cooling, the tube was covered with a few layers of gauze and centrifuged for 15 minutes at 2500 r.p.m. The supernatant fluid was removed by decantation or siphoning and was analyzed for iodine. This fraction was designated as inorganic, or "I" iodine. The protein precipitate was washed once with the same volume of 0.02 normal acetic acid as was used in the precipitation. After a second centrifugation the supernatant liquor was discarded and the protein precipitate was analyzed for iodine; this fraction was designated as the protein-bound or "P" iodine. When it seemed likely that the inorganic fraction was unusually high, as discussed later, the protein coagulum was washed four times in the same manner.

Inorganic Iodine. The values for "inorganic" iodine of human plasma were obtained as described above and are shown in Figure 1. The inorganic iodine, "I," constitutes roughly one-third of the normal total plasma iodine as determined by this method. It varies between 0.5 and 4 $\mu\text{g.}$ per 100 cc.; the mean value is approximately 2 $\mu\text{g.}$ per 100 cc. It is apparent that the value of inorganic iodine is relatively constant despite wide variations of thyroid activity. The inorganic iodine, however, is increased markedly whenever the patient receives unusual amounts of iodine from an external source. Such sources may be diets high in iodine, medication, external applications of iodine to the skin, inhalation of

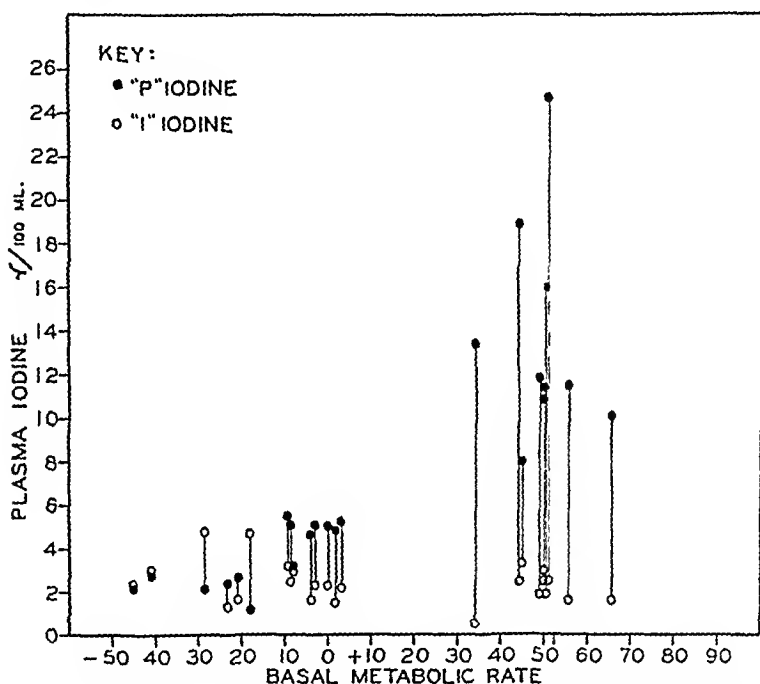


FIG. 1.—In cases ranging from myxedema to marked hyperthyroidism, the inorganic "I" iodine tends to remain constant, although the protein-bound "P" iodine rises as thyroid activity increases.

iodine vapors or diagnostic procedures employing radio-opaque materials rich in iodine. Under such circumstances the inorganic iodine may reach values exceeding 1000 $\mu\text{g.}$ per 100 cc. In one instance tincture of iodine applied to the skin in preparation for lumbar puncture was sufficient to raise the inorganic iodine to nearly 2000 $\mu\text{g.}$ per 100 cc. The elevation of "I" iodine, however, following a "standard dose"* of iodine tends to be less marked in cases of hyperthyroidism than in euthyroid or hypothyroid cases. This point will be discussed later.

PROTEIN-BOUND IODINE. Distribution of "P" Iodine in Successive Fractions of the Plasma Proteins. McMeekin¹¹ has described the

* Five minims of saturated solution of potassium iodide daily for 6 days.

precipitation *serialim* of successive protein components of horse serum through the use of ammonium sulphate. In the present studies such fractions, obtained through the courtesy of Dr. McMeekin and also prepared in this laboratory by his procedure, were analyzed for total protein and for protein-bound iodine. The fractions were separated at approximately the following concentrations of ammonium sulphate: 1.6 M., * 2.1 M., 2.8 M. and 4.0 M. In addition, the albumin fraction soluble at 2.1 M., but insoluble at 2.8 M. was further fractionated into two subfractions, (a) that removed at 2.4 M. and (b) that removed at 2.8 M. The former of these two was fractionated further by removal of crystalalbumin. In this manner a spectrum of the plasma or serum was obtained showing simultaneous distributions of proteins and protein-bound iodine.

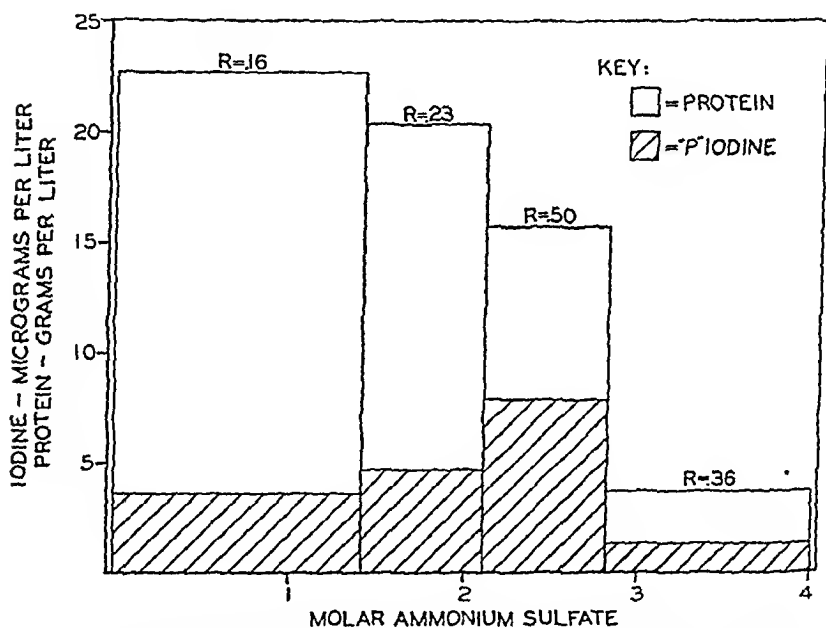


FIG. 2.—When plasma protein fractions are preprecipitated *serialim* at increasing concentrations of ammonium sulphate, the natural protein-bound iodine is found to reside prominently in the traditional albumin fraction. The results illustrated are for horse serum.

The results shown in Figure 2 were obtained with horse serum. It is evident that the globulin fractions precipitated by a molarity of 1.6 contain little protein-bound iodine. Slightly more appears in the upper globulin fractions, which are precipitated by a molarity of 2.1. The bulk of the protein-bound iodine, however, is associated with the "crude" albumin fractions precipitated below a molarity of 3.0. The proteins soluble in that concentration of ammonium sulphate did not

* M. = molar.

contain an important amount of protein-bound iodine. The ratio of iodine to protein (micrograms of iodine per gram of protein) rose successively to a maximum value of 0.8 in the albumin fraction soluble at 2.4 and insoluble at 2.8, *i. e.*, in a rather sharply defined fraction. The crystalalbumin fraction, however, contained relatively little protein-bound iodine.

Similar studies on human plasma have yielded comparable results. These are reported in detail elsewhere.¹⁷ The total plasma protein-bound iodine in a sample of pooled human plasma was found to be 5.2 $\mu\text{g.}$ per 100 cc. In this instance the crude proteins had been precipitated and prepared as a dry powder. For comparison, in a series of 10 normal control individuals the plasma protein-bound iodine values ranged from 4.6 to 5.9 $\mu\text{g.}$ per 100 cc., as determined by the technique described earlier in this report; their mean was 5.2.

It should be noted that from a strict physicochemical standpoint, the partially purified protein fractions illustrated in the figure are still crude, even though they represent a considerable technical advance over the older, traditional method of separation which continues to be described in the literature.¹⁸ In other words, it is conceivable that a small amount of specialized iodoglobulin may be responsible for the high iodine content found in our crude "albumin" fractions. It must be noted, however, that in a preparation of human albumin which appeared to be 100 per cent albumin by electrophoresis measurements, a very high iodine concentration was found.

This last-mentioned material was prepared by Dr. S. H. Armstrong, Jr. in the laboratory of Prof. E. J. Cohn. A detailed account of these observations will be found elsewhere,¹⁷ but a brief summary may be given to illustrate the general procedure. Iodine was determined in the several crude protein fractions separated from whole human plasma by ethanol under special precautions. Per gram of protein, the iodine content in micrograms of these fractions was as follows: I, fibrinogen 0.2; II, first globulin fraction 0.2; III, intermediate globulin fraction 0.3; IV, alpha and beta globulins 1.2; V, main albumin fraction 0.9; VI, residual albumin, 0.8. These data reflect those obtained with ammonium sulphate in that 58% of the total protein-bound iodine appeared in the main albumin fraction, V, as compared with 46% in the ammonium sulphate separation; but the highest ratio appeared in the fraction containing alpha and beta globulins. When Fractions IV and V were purified further, the ratios were as follows: for α - β globulins 1.7; for albumin 1.4. These last two values are especially significant because electrophoretic measurements showed the α - β globulins to contain less than 5% of albumin and the albumin fraction to contain no perceptible globulin. In short, even after rather careful precautions to obtain homogeneous α - β globulin and albumin fractions, respectively, high concentrations of iodine were found in

both. Possibly the former contained slightly more iodine per gram of protein, but considerably less in terms of the total mass of protein.

Collateral observations indicate that there are several albumins in human plasma, and that the iodine is preferentially allocated to one or more of these fractions.

Relationship of "P" Iodine to "I" Iodine. As described above, after iodine medication or other contact with iodine-containing material, the plasma iodine is increased. When the inorganic iodine rises far above normal, the apparent protein-bound iodine also is elevated. As demonstrated in Figure 3, the protein-bound

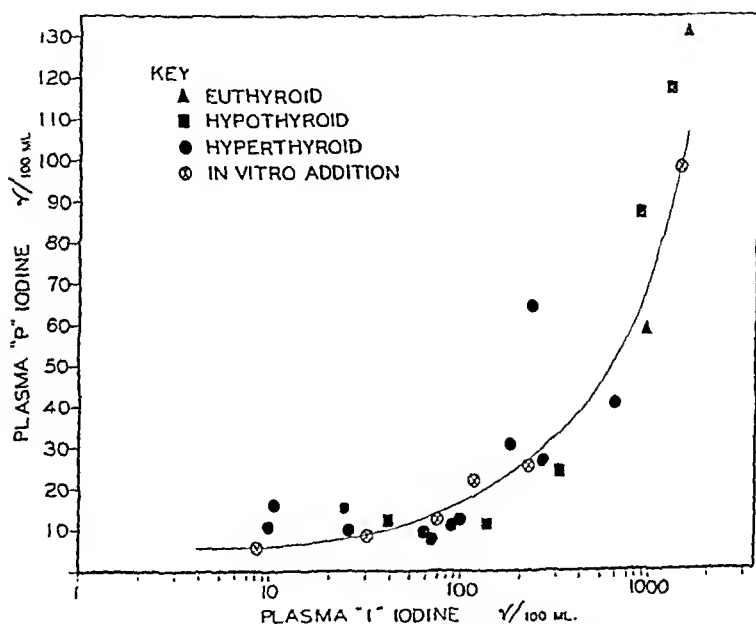


FIG. 3.—A spurious elevation of the protein-bound "P" iodine occurs when the inorganic "I" iodine is unusually high, as described in the text.

iodine, "P," is roughly proportional to the inorganic iodine value, "I," determined simultaneously. This is true irrespective of the state of thyroid function, although, as already mentioned, there is some tendency for hyperthyroid individuals to show lower levels of inorganic iodine than do normal or myxedematous patients on comparable doses of iodide, and hence a lower "P" iodine value.

This elevation of protein-bound iodine which accompanies elevation of the inorganic fraction can be duplicated *in vitro* by the addition of potassium iodide in increasing amounts to normal human plasma. Such an experiment is illustrated in Figure 3. As indicated by the smooth curve, the values obtained *in vitro* are

entirely comparable with the values determined for random samples of blood from patients receiving therapeutic doses of iodine.

The mechanism by which this spurious elevation of plasma "P" iodine occurs is not clear. It may be due to occlusion or adsorption, and thus might be regarded as a chemical artefact. In any case, it constitutes a technical hazard which must be avoided in evaluating levels of plasma "P" iodine. If the inorganic "I" iodine is found to be unusually high, the plasma "P" iodine value must be considered as meaningless, at least for the present.

Response of Plasma Iodine to Thyroxine Therapy. When crystalline thyroxine in solution is administered to a patient, a persistent rise in the plasma "P" iodine value occurs. This effect is illustrated by a case of exophthalmic ophthalmoplegia³ in a male of 36 years, whose exophthalmos receded strikingly during treatment with thyroxine. Before and during therapy, basal metabolic rate and "P" iodine values were determined. These data were as follows:

Date.	mg. Thyroxine therapy.	B. M. R.	Plasma.		Exophthalmos by Luedde ophthalmometer (mm.)	
			"P" iodine (μ g. per 100 cc.)	"I" iodine (μ g. per 100 cc.)	O.D.	O.S.
2/13	None	-10	5.6	4.9	24	23 5
4/7 to 4/11 inc.	1 mg. i.v. daily	-5	10 3			
4/12 to 4/15 inc.	1 mg. i.v. daily	-8				
4/16	10 mg. i.v.					
4/17	10 mg. i.v.					
4/18 to 4/22 inc.	10 mg. i.v.					
5/1	None	+34	18.0	3.9	18	17 5
5/28	18	18 5

Relationship of "P" Iodine to Thyroid Status. As illustrated in Figure 1, the plasma protein-bound "P" iodine tends to vary directly with the basal metabolic rate or possibly as the antilogarithm of the basal caloric consumption. The values in hypothyroidism may be less than 1 mg. per 100 cc. and the mean is 2 mg. per 100 cc.; in euthyroidism the levels range between 4 and 8 mg. per 100 cc.; and in hyperthyroidism the values exceed 8 mg. per 100 cc. A detailed study of "P" iodine in thyroid disease is presented elsewhere¹⁵ and in the companion report immediately following this communication.

Fractions of Protein-bound Iodine Resembling, Respectively, Thyroxine and Diiodotyrosine. Elmer, Luczynski, Rychlik and Schepps⁴ obtained large quantities of human blood pooled from different patients and hydrolyzed it after the manner of Leland and Foster.⁹ They estimated that approximately 40 to 60% of the "organic" iodine in normal blood behaved like thyroxine. Similar values were obtained in blood from hyperthyroid individuals. Likewise Trevor²⁰ reported that about one-third of the protein-

bound iodine in the plasma of animals had properties like thyroxine, whereas the remainder behaved like diiodotyrosine.

In the present studies these "T" and "D" fractions were estimated in the following fashion:

Proteins were precipitated from 10 cc. of plasma, as described previously, and then suspended in 10 cc. of water to which had been added approximately 20 mg. of commercial pepsin (Merek), 0.5 cc. of 18 N sulphuric acid and 5 drops thymol blue. This mixture was digested at 37° C. in a 50-cc. centrifuge tube until the contents were liquid; *i. e.*, for 12 to 24 hours. Acid was added as necessary to keep the digest at pH 1.5. After digestion the pH was raised to 2.5 and the mixture extracted with a volume of butyl alcohol equivalent to twice the volume of plasma originally used. Centri-

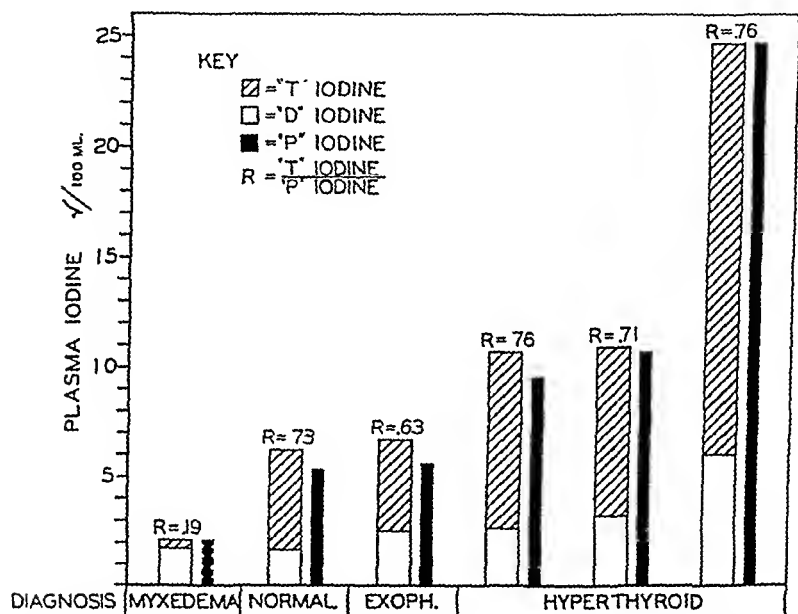


FIG. 4.—In cases ranging from myxedema to marked hyperthyroidism, the absolute rise in protein-bound "P" iodine is due largely to an elevated thyroxine-like "T" fraction.

fugation at 3000 r.p.m. separated the solutions. A gel frequently formed in the butyl alcohol layer, but after being broken up by jarring or with a stirring rod, centrifugation reduced it to a small precipitate located at the interphase. The butyl alcohol layer was then withdrawn and the water layer was re-extracted with one-half the volume of butyl alcohol used before. After centrifugation this butyl alcohol layer was added to the first butyl alcohol extract. Any precipitate which remained at the interface was carried along with the butyl alcohol. The water layer which remained was discarded. The combined butyl alcohol extracts were shaken with an equal volume of 2 N sodium hydroxide containing 5% sodium carbonate in separatory funnels which could be centrifuged in special trunnion carriers at 1000 r.p.m. After this centrifugation the alkaline layer was removed and the butyl alcohol layer reextracted with one-half the original volume of alkali. After another centrifugation the alkaline layer was withdrawn

and added to the first alkaline extract. This alkaline aqueous solution was designated as the D-fraction and was analyzed for its total iodine content.

The butyl alcohol layer was evaporated to dryness and 25 cc. of water was added. This solution was designated as the T-fraction and was analyzed for its total iodine content.

As shown in Figure 4, illustrating a series of plasma values from patients with myxedema and hyperthyroidism as well as from normal individuals, the D-fraction represents about 30% of the "P" value; in absolute terms this varies from 1 to 6 mg. per 100 cc. In normal individuals the T-fraction is approximately twice the D-fraction. This T-fraction, however, varies with the thyroid status of the individual, tending to be practically absent in myxedema and excessively large in severe hyperthyroidism. Indeed, the marked variations of the protein-bound iodine with varying physiologic thyroid status, to be discussed in the subsequent paper, are probably in large measure due to changes in the T moiety.

The efficiency of the method in recovering thyroxine, when added to water as well as to human plasma, is demonstrated by the data in Table 2. When thyroxine is added to plasma, not only is it recovered entirely as protein-bound iodine, as reported also by Trevor²⁰ but it contributes exclusively to the "T" fraction.

TABLE 2.—THYROXINE-LIKE AND DIIODOTYROSINE-LIKE COMPONENTS OF PROTEIN-BOUND "P" IODINE.

Solvent.	Addition.	Protein-bound "P."	Thyroxine-like "T."	Diiodotyrosine-like "D."
Water . . .	0.65 µg. per 100 cc. thyroxine	..	0.5 µg. per 100 cc. (75% recovery)	
Water . . .	0.59 µg. per 100 cc. diiodotyrosine	0.54 µg. per 100 cc. (92% recovery)
Human plasma	None	6.0	5.5	1.5
Human plasma	5.6 µg. per 100 cc. thyroxine	11.9	11.2	2.0

Discussion. It should be emphasized that the methods described here have been simplified for clinical use, and may not be universally applicable to problems of a more fundamental type. For example, all of the plasma proteins have been precipitated routinely, whereas the naturally circulating iodine resides prominently in the crude albumin range. The chief precautions which have proved essential to uniformity of results have been: 1, overnight fasting; 2, the use of plasma instead of whole blood; 3, the elimination of incoagulable, "inorganic" iodine; and 4, the exclusion of unusual contamination from iodine-containing material.

As described, the method *in toto* requires careful work but no complicated apparatus. As the microdetermination of iodine becomes further improved and simplified, it seems likely that this

general procedure may become a routine test in large clinics which deal with endocrinologic problems.

At present, the method is not applicable without special precautions when gross contamination with iodine has occurred within 3 weeks. Routine therapy with Lugol's solution, diodrast kidney clearance tests, cholecystography or the painting of iodine upon the skin represent hazards which vitiate the "P" iodine determination. In case of doubt, the "I" iodine should be determined simultaneously, and if it is above 5 or 6 $\mu\text{g.}$ per 100 cc., the "P" iodine value should be viewed with distrust.

Too great stress should not be placed upon the absolute values for iodine concentration stated here. Such values are relative and depend upon the technique involved. Estimations of the apparent iodine concentration of the blood, as reported from various laboratories, have been falling steadily for two decades, and may still vary somewhat in different laboratories. Fortunately, however, the reported range of normal values has become rather stable in the past few years. Each institute should learn and state clearly its own range for normal values.

Within these limitations, the determination of "P" iodine appears to be a practical and useful method for clinical investigation and routine diagnosis, because it affords at least a roughly quantitative measurement of the circulating thyroid hormone. As endocrinology rapidly is becoming a subdivision of the medical sciences that is being studied quantitatively, the need for such precise measurements of hormone concentration in biological and clinical material is obvious.

Summary. The protein-bound iodine in the blood plasma of man and of animals was found to reside chiefly in the traditional albumin fraction. This iodine was subject to fluctuations dependent upon thyroid activity. Such fluctuations, in absolute terms, were due chiefly to a thyroxine-like moiety thereof. The moiety resembling diiodotyrosine might increase proportionately, but it contributed relatively little to the absolute change from the normal level. Accordingly, total protein-bound iodine fluctuated largely with thyroxine-like iodine. In myxedema, the thyroxine-like fraction practically disappeared.

Despite variations in this protein-bound iodine, the ionized iodine (inorganic) appeared to be rather low and approximately constant under the conditions of our study, regardless of the state of thyroid activity. Nevertheless, it was found to increase markedly when extraordinary, though perhaps very small, amounts of iodine entered the organism. Simultaneously a false increase in the protein-bound iodine occurred which could be reproduced by the addition of iodide to plasma *in vitro*.

The results indicate that the protein-bound thyroxine-like moiety of the plasma iodine is a good objective index of circulating thyroid

hormone. They suggest, also, that plasma protein-bound iodine might be used clinically to confirm physiologic thyroid status. This application to cases of thyroid disease will be described in the communication immediately following.

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PROTEIN-BOUND IODINE IN BLOOD.

VI. ITS RELATION TO THYROID FUNCTION IN 100 CLINICAL CASES.*

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In the preceding communication¹ it was suggested that the protein-bound iodine of blood plasma might be used as an index of

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This investigation was aided by grants to William T. Salter from the Milton Fund of Harvard University and from the Committee on Research in Endocrinology of the National Research Council.

the circulating thyroid hormone. In this way a quantitative estimate of effective thyroid activity might be gained. It is the purpose of the present report to describe the results so obtained in 100 clinical cases.

Inasmuch as the significance of the blood iodine has been discussed in detail elsewhere,¹⁸ only a few outstanding examples of recent clinical studies will be cited. As regards total blood iodine, important series of cases have been reported by Perkin and Lahey,¹⁴ by Turner, DeLamater and Province¹⁹ and by Riggs, Gildea, Man and Peters.¹⁷ Perkin and Hurxthal¹³ and McClendon, Foster and Kirkland⁸ have also studied the so-called "organic" iodine fraction as determined by separation with organic solvents like alcohol and acetone. In general, all of these series, one of which comprises over 1000 cases,¹⁴ show a distinct tendency on the part of the blood iodine level to vary directly with thyroid activity. In all, however, with the partial exception of the recent series of Riggs and his associates,¹⁷ certain grave difficulties in interpretation have been encountered. For example, in myxedema the values have often fallen within a low normal range, as pointed out recently by Greene.⁵ Likewise in the large series reported by Perkin, Lahey and Cattell¹⁵ many cases of Graves' disease showed a normal blood iodine concentration and a smaller percentage of normal individuals showed a high blood iodine value. In fact, Perkin and Cattell¹² have emphasized this discrepancy as an aid in deciding upon the therapeutic procedure to be employed.

Because of these discrepancies, *plasma protein-bound iodine* has been determined in 100 cases of suspected thyroid disturbance, in the hope that careful scrutiny of a relatively small number of cases might reveal correlations and reasons for lack of correlation.

Methods. Blood for the determination of plasma protein-bound iodine was drawn after overnight fasting and, whenever possible, immediately following determination of the basal metabolism. Special precaution was taken to be sure that no thyroid or iodine therapy had been used within the preceding 3 weeks, and the latter therapy was excluded in doubtful cases by a simultaneous determination of the plasma ("inorganic") iodide. The chemical methods used have been described in detail in previous communications.^{1,15}

The basal metabolic rates were determined with the Benedict-Roth apparatus under the usual standard conditions as described by Dubois and Benedict. The normal standards employed were those of Dubois as prepared by Boothby and Sandiford at the Mayo Clinic.

Classification of Cases Studied. For euthyroid controls, 10 individuals were selected, half of them healthy laboratory workers and the other half patients in whom no suspicion of thyroid disturbance was entertained.

Each of the 100 test cases received individual evaluation and was classified on the basis of: 1, ultimate clinical diagnosis; 2, ultimate or most trustworthy basal metabolic rate, and 3, microscopic appearance of the thyroid gland, when available. This classi-

fication was made without knowledge of the plasma iodine concentration. It was thus possible to distribute the 100 cases into four main clinical subgroups; *i. e.*, hypothyroid, euthyroid,* hyperthyroid and ophthalmic cases (Table I). The latter group consisted of so-called "Graves' disease without hyperthyroidism"¹⁰ or "exophthalmic ophthalmoplegia."² This latter syndrome is discussed in detail below. For future reference, a census of the cases studied has been appended.

TABLE 1.—DISTRIBUTION OF CASES STUDIED.

Diagnosis.	No. of cases.	B.M.R.	"P" iodine vs. diagnosis	
			Com- patible.	Incom- patible.
<i>Series I. Compatible Diagnosis and B.M.R.</i>				
A. Hypothyroid	20	Low	20	0
B. Euthyroid	5	Standard	5	0
C. Hyperthyroid	38	High	37	1
D. Ophthalmic	8	Standard	8	0
Total	71		70	1
<i>Series II. Incompatible Diagnosis and B.M.R.</i>				
A. Euthyroid	9	Low	9	0
B. Euthyroid	12	High	12	0
C. Ophthalmic	5	Low	4	1
D. Ophthalmic	2	High	2	0
E. Hyperthyroid	1	Standard	1	0
Total	29		28	1
Grand total	100		98	2
<i>Control Series</i>				
Euthyroid	10	Standard	10	0

From such a classification certain interesting correlations appeared which served as the basis for further analysis. Nearly all the cases adjudged euthyroid had plasma protein-bound iodine values greater than 3.9 $\mu\text{g.}$ per 100 cc. and less than 8.1 $\mu\text{g.}$ per 100 cc. (see Figs. 1 and 2), and these figures were selected arbitrarily as the limiting values of the euthyroid state. The criteria for the basal metabolic rate used here were as follows: Less than 10% was considered to be substandard, from -10 to +15%, inclusive, was called normal and greater than 15% was called elevated. It was also apparent that evaluation of the plasma protein-bound "P" iodine would be facilitated by regrouping the 100 cases into two series, as follows: On the basis that for each case, one of the above described clinical diagnoses and the truest estimate of basal metabolic rate were either compatible or incompatible, the cases were segregated into Series I and Series II, respectively. For example, a case of obvious myxedema with a basal metabolic rate of -40

* A euthyroid individual is one whose tissues at large receive the normal amount of thyroid hormone daily, irrespective of the anatomic state of the thyroid gland.

was placed in Series I. On the contrary, a case diagnosed clinically as euthyroid with a basal metabolic rate of +40 (before iodine or other therapy) was placed in Series II. These two series are referred to as the "compatible" Series I and the "incompatible" Series II, respectively.

Obviously, Series II requires the greater scrutiny. The standard diagnoses were therefore subdivided further into subgroups (A, B, C, D and E) according to the nature of the discrepancy involved (Table 1). Typical and representative cases in each of the subgroups will be presented later.

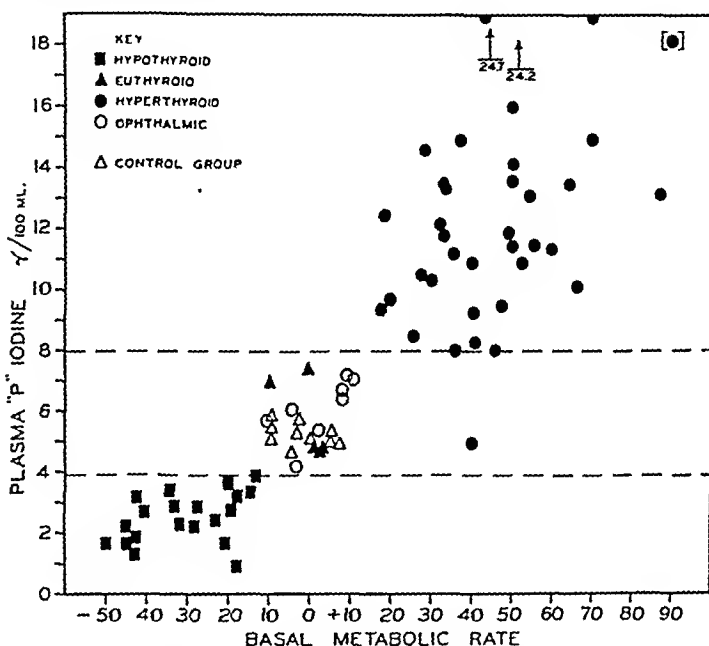


FIG. 1.—In two-thirds of the test cases studied, the clinical diagnosis and the basal metabolic rate were compatible, as shown in the figure. Plasma protein-bound iodine values are given for these cases and for 10 euthyroid controls. The "ophthalmic" cases are described in the text.

On the basis of these classifications and with the arbitrary standards for plasma protein-bound iodine and basal metabolic rate stated, it was possible to compare the clinical, metabolic and blood iodine findings in order to ascertain the significance of the latter.

Analysis of Cases by Clinical Groups. SERIES I: CLINICAL DIAGNOSIS AND BASAL METABOLIC RATE COMPATIBLE. This group, illustrated in Figure 1, comprises 71 cases, or 71% of the total number.

Hypothyroid. As shown in Figure 1, 20 cases of hypothyroidism were included in this category and all had plasma protein-bound

iodine values of less than 4 $\mu\text{g.}$ per 100 cc., *i. e.*, definitely subnormal. This suggests that plasma protein-bound iodine is of distinct value in confirming the diagnosis of poor thyroid function, particularly in those cases in which full-blown myxedema is not present. Heretofore such cases often have been indistinguishable from the normal when whole blood iodine⁵ or "organic" iodine⁶ has been measured.

Controls. As previously stated, 10 euthyroid controls were added to the series of 100 test cases. As shown in Figure 1, all 10 had plasma protein-bound iodine values greater than 4 $\mu\text{g.}$ per 100 cc. and less than 8 $\mu\text{g.}$ per 100 cc. In this way "normal" values were defined.

Euthyroid Cases. Likewise 5 cases, who at first were suspected of thyroid disease despite normal basal metabolic rates but who were diagnosed finally as euthyroid, all had "normal" plasma protein-bound iodine values.

Hyperthyroid. In Figure 1 are charted also 38 cases of hyperthyroidism. All but one had plasma protein-bound iodine values exceeding 8.0 $\mu\text{g.}$ per 100 cc. On the whole, the elevation of the iodine level tended to be proportional to the elevation of the basal metabolic rate, but individual exceptions were not infrequent. It should be stressed that in each of the above cases of hyperthyroidism, *at the bedside* it was decided that the patient showed sufficient evidence of both (1) neurologic and (2) calorigenic disturbance to warrant the diagnosis of Graves' disease with hyperthyroidism.

Ophthalmic. The ophthalmic cases include the syndrome defined by Means¹¹ and Salter¹⁸ as "Graves' disease without hyperthyroidism." These authors have noted the absence of calorigenic disturbances (warm, moist skin; excessive sweating and weight loss) in cases which otherwise resemble classical Graves' disease. Accordingly, they suggest that despite the neurologic symptoms, such cases are in effect euthyroid and have basal metabolic rates which usually are normal or substandard. In addition, the electroencephalogram may show normal alpha cortical rhythm and reaction time.³ The majority of these cases exhibit marked exophthalmos and have been described by Brain² as "exophthalmic ophthalmoplegia." Occasionally cases of malignant exophthalmos display clinical and metabolic evidence indicating that they are hyperthyroid or hypothyroid, and in this report are classified as such; in other words, the classification "ophthalmic" has been reserved only for those cases adjudged to be euthyroid.

Eight ophthalmic cases are represented in Figure 1; all had normal basal metabolic rates and all had normal plasma protein-bound "P" iodine values. A representative case history follows.

CASE 66.—B. H. (B. C. H. No. 1017062), a 36-year-old male stationary engineer entered the hospital, complaining of bilateral prominence of his

eyes and conjunctivitis of 7 months' standing. There was no change in appetite nor loss of weight. There was no goiter, tremor or tachycardia. The skin was normal. The basal metabolic rate was -10% . Measurement of the eyeballs with the Luedde exophthalmometer⁷ showed the cornea to be 24 mm. anterior to the lateral orbital margin. Plasma protein-bound iodine was 6.4 $\mu\text{g.}$ per 100 cc. After 3 weeks of therapy with large doses of thyroxine the basal metabolic rate rose to $+34\%$ and the plasma protein-bound "P" iodine to 18 $\mu\text{g.}$ per 100 cc. During this time the eyeballs receded 7 mm. and the chemosis and inflammation subsided.

The favorable course of the exophthalmos when the circulating plasma iodine was artificially elevated is, of course, consistent with the thesis that Graves' disease and physiologic hyperthyroidism may be dissociated. Indeed, although there is still considerable dispute as to the appropriate therapy in these cases, recent publications^{4,11} have suggested that thyroxine or thyroid medication is superior to thyroidectomy, which may accentuate the exophthalmos to an alarming degree.

In addition to idiopathic cases of exophthalmic ophthalmoplegia, the "ophthalmic" group here reported includes both patients who have submitted to thyroidectomy and also chronic cases of physiologic hyperthyroidism which have "burned out." Because cases of Graves' disease apparently may show all intergrades of thyroid activity, it is obvious that the selection of the euthyroid cases taxes clinical judgment to the point of arbitrary decision. As will appear presently, however, such crude judgments have sufficed for present purposes.

In summary, the over-all correlation of basal metabolic rate with plasma protein-bound iodine in Series I is very high, namely, 0.82 ± 0.05 for the 71 cases plus the 10 controls, totaling 81 individuals. The statistical P-value is less than 0.001. As the cases in this series are quite straightforward as regards their diagnosis, there is little need to discuss them further. There remain, however, 29% of the cases which must be classified otherwise.

SERIES II: CLINICAL DIAGNOSIS AND BASAL METABOLIC RATE INCOMPATIBLE. This series consists almost entirely of individuals who were adjudged euthyroid on general clinical grounds, but who showed an abnormal basal metabolic rate. In certain cases it might be surmised that the recorded metabolism was not truly basal, but it was the best value obtainable after repetition under routine conditions in a large hospital. These cases are recorded as Series II in Table 1 and they are charted in Figure 2. Characteristics and representative cases of each of these subdivisions (see Table 1) follow.

SERIES II-A: EUTHYROID INDIVIDUALS WITH SUBSTANDARD BASAL METABOLIC RATE. In this subgroup are included 9 cases with a basal metabolic rate below -10 , in whom no definite clinical evidence of hypothyroidism could be discovered. It is concluded that these individuals represent cases of a substandard but physio-

logically normal basal metabolic rate. In 2 cases the diagnosis was hypopituitarism with secondary hypogonadism. Despite basal metabolic rates of -20 and -30% , respectively, their lack of clinical evidence of hypothyroidism and their negligible response to thyroid medication seemed to warrant a diagnosis of euthyroidism. All of these cases had normal plasma protein-bound iodine values. A representative case follows in summary.

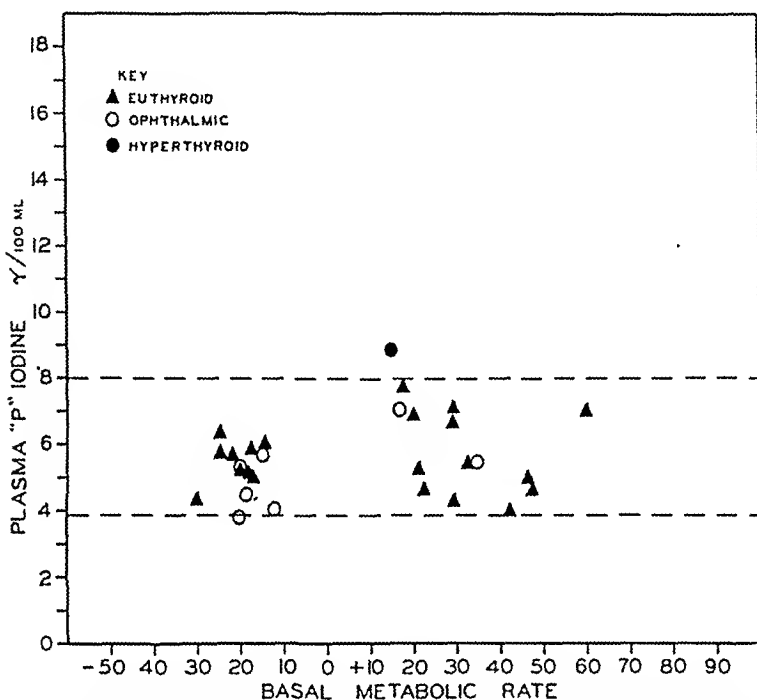


FIG. 2.—In approximately one-third of the test cases the basal metabolic rate determination was incompatible with the final clinical diagnosis. Most of these cases had a normal plasma protein-bound iodine, as shown in the figure. The "ophthalmic" cases are described in the text.

CASE 75.—J. O'S. (B. C. H. No. 1004320), a 36-year-old male clerk, entered the Boston City Hospital complaining of nervousness, sweating, insomnia and loss of weight. He appeared very nervous, had a constant tachycardia and a slight manual tremor. His thyroid was of normal size and his skin, though of fine texture and moist, was quite cool. Hyperthyroidism was suspected at first but his basal metabolic rate was -22% . Certain psychic problems were uncovered and when corrective measures were instituted marked symptomatic relief followed.

SERIES II-B: EUTHYROID INDIVIDUALS WITH ELEVATED BASAL METABOLIC RATE. This group of 12 cases comprised patients suffering from cardiac decompensation, neurasthenia or hyperpyrexia, in whom the possibility of hyperthyroidism was considered at first on general clinical grounds and apparently confirmed by the finding of an elevated basal metabolic rate. In these cases, however, relief of the underlying condition, *e. g.*, circulatory failure

or anxiety, sufficed to return the basal metabolic rate to normal without specific iodine therapy. In the few cases in which a therapeutic trial of iodine alone was made, it proved ineffective in correcting the symptoms or in lowering the elevated metabolic rate. Thus the course of the illness caused abandonment of the initial impression of hyperthyroidism. All the patients in this group had normal plasma protein-bound iodine levels. A representative case follows.

CASE 86.—P. McK. (B. C. H. No. 967590), a 52-year-old policeman, entered the hospital complaining of dyspnea and edema of the ankles. The blood pressure was 190/110 mm. Hg. Hyperthyroidism was suspected because of restlessness, staring eyes and pink complexion of the face. Attempted basal metabolic rate readings yielded approximately +40% on repeated determinations. After several weeks of rest in bed and treatment with digitalis, the initial symptoms of anxiety abated as the circulation improved and the basal metabolic rate became normal.

SERIES II-C: OPHTHALMIC CASES WITH SUBSTANDARD BASAL METABOLIC RATE. This group of 5 cases was composed of patients who, as described above, presented marked exophthalmos and, in some cases, neurologic symptoms of Graves' disease, but no disturbance of caloric balance. They were all considered to be euthyroid despite substandard basal metabolic rate. A characteristic case follows.

CASE 95.—M. C. (B. C. H. No. 1028107), a 39-year-old American housewife, entered the hospital with a history of diplopia, vertigo and sudden exophthalmos of 1 month's duration. Two years previously she had a thyroidectomy for typical thyrotoxicosis, and thereafter until her recent illness had been in excellent health. Examination disclosed a well nourished woman with marked exophthalmos, lid lag and convergence defect. Moderate periorbital edema was present. Her speech and movement were quick and nervous. The skin was of normal texture and temperature, but dry. Her heart rate was normal and she had no tremor. Basal metabolic rate was -20%.

All but one of these cases had normal plasma protein-bound "P" iodine values. The exception occurred in an ophthalmic case which had developed following thyroidectomy for thyrotoxicosis. The basal metabolic rate was -20%. Although mild hypothyroidism was suspected at first, the patient was finally judged to be euthyroid. His plasma protein-bound iodine value was barely subnormal (3.9 μ g. per 100 cc.).

SERIES II-D: OPHTHALMIC CASES WITH HIGH BASAL METABOLIC RATE. Cases so classified present peculiar difficulties in diagnosis. Obviously the designation of clinical euthyroidism is challenged by the presence of neurologic symptoms, exophthalmos and elevated basal (?) metabolic rate which may characterize these patients in varying degree. In such borderline cases two equally experienced clinicians may disagree at the bedside as to the evidence for or against normal or increased metabolism. Fortunately there were

only 2 such cases in the series. Because the clinical evidence for abnormally high caloric consumption was unconvincing, they were classified as euthyroid, without knowledge of the plasma iodine concentration. The problems in diagnosis and the evidence for adjudging them euthyroid are well exemplified in the following case.

CASE 99.—M. B. (B. C. H. No. 990460), a 41-year-old widow entered the hospital complaining of sciatica and nervousness. A diagnosis of hypertensive cardiovascular disease and anxiety state was made. She reentered several months later, complaining of increasing irritability, excessive sweating when nervous, and palpitation. Her cardiovascular status was unchanged except for the presence of tachycardia; her thyroid was normal to physical examination, and although she had slight exophthalmos no associated eye signs were present. Her initial basal metabolic rate was +36%. After this single determination of metabolic rate the patient received iodine therapy, following which her apparent basal metabolic rate fell to +9% without coincident improvement in symptoms. During the next few months she took iodine intermittently at home, and on her third entry presented essentially the same findings as on previous discharge. Again the metabolic rate was elevated and again simultaneous bed rest, reassurance and iodine caused it to return to normal. Thyroidectomy was performed and the pathologic diagnosis was reported by one pathologist as: colloid goiter; by Dr. Shields Warren as: longstanding hyperinvolution of old primary hyperplasia—not the result of recent iodine medication.

Despite her subtotal thyroidectomy the patient experienced no relief from her complaints of nervousness, tachycardia and sweating, for which she was hospitalized again 9 months after her operation. Physical findings, except for absent thyroid gland, were unchanged from her previous entries and again the basal metabolic rate was +40%. This time, however, iodine was withheld and on bed rest alone the basal metabolic rate returned to normal. Prior to her thyroidectomy, at a time when the basal metabolic rate had been +36%, her plasma protein-bound iodine level was normal (5.5 $\mu\text{g.}$ per 100 cc.), and therefore consistent with the diagnosis one would be forced to make in retrospect, *i. e.*, Graves' disease *without* hyperthyroidism.

The other case in this group also had a normal plasma protein-bound iodine value.

SERIES II-E: HYPERTHYROIDISM WITH NORMAL BASAL METABOLIC RATE. This category is represented by one case of recurrent hyperthyroidism, recognized clinically as "mildly toxic," in which the basal metabolic rate was +14%. It falls, therefore, into the incompatible group, although obviously the estimation of physiologic status was a borderline decision. Interestingly enough, the plasma protein-bound iodine was only slightly above the normal limit, *i. e.*, 8.8 $\mu\text{g.}$ per 100 cc.

Comment. Of the cases shown in Figure 2, those in Series II-A, II-B, II-C and II-D may properly be considered to be euthyroid on clinical grounds, and in all but one of these cases the plasma protein-bound iodine was actually normal. It should be remarked that this second large series, if combined with the first series, would distort the correlation between the basal metabolic rate and plasma iodine determination as indices of abnormal thyroid function. In

fact, such a combination might lead to the same conclusion that previous series have led to, namely, that a poor correlation exists between basal metabolic rate and blood iodine concentration. In the present instance, however, the coefficient of correlation for the entire 100 cases would be reduced only to 0.79 ± 0.04 .

Recrudescent Hyperthyroidism. In order to evaluate a biochemical procedure like plasma protein-bound iodine, it is obviously necessary to crowd one's test cases into a simplified rigid scheme of classification as regards diagnosis. In this process, difficult diagnostic situations occasionally arise which require very arbitrary treatment. For example, such a case may be in spontaneous remission when first studied, and may later show clinical evidence of excessive caloric turnover, together with an elevated basal metabolic rate and high plasma iodine level. A synopsis of such a case follows.

CASE 83.—M. N. (B. C. H. No. 965392), a 44-year-old Greek housewife, entered the hospital complaining of palpitation, shortness of breath and edema of the ankles of several months' duration. Examination showed a thin, anxious woman in obvious congestive failure without auricular fibrillation. There was no goiter, tremor or marked exophthalmos. Blood pressure was 160/95. After several weeks of treatment with digitalis and rest, cardiac compensation was restored. The basal metabolic rate, however, remained close to +40% and the pulse over 80. Plasma protein-bound iodine was 6 $\mu\text{g.}$ per 100 cc. A therapeutic test with iodine did not alter the basal metabolic rate, which was determined with some difficulty because of the patient's apprehension and mild orthopnea. The patient was discharged on iodine therapy and given a course of Roentgen ray treatments to the thyroid region. Ten months later she reentered, presenting much the same picture as at the previous admission. At this entry, however, the thyroid was definitely palpable, a little more prominent on the right, and the thyroid isthmus seemed hyperplastic. After restoration of cardiac compensation the basal metabolic rate rose steadily from +30% to +55% in 3 weeks. At this time the plasma protein-bound iodine was found to be 10 $\mu\text{g.}$ per 100 cc. Routine treatment with Lugol's solution was begun and in 2 weeks the basal metabolic rate had fallen to +25%. A clinical diagnosis of toxic nodular goiter was made.

The question might be raised by some clinicians whether this case was originally one of "burned out" hyperthyroidism in which iodine therapy had supplied new building material wherewith the thyroid gland could manufacture again an excess of hormone. In other words, the mechanism involved would resemble that of "Jod Basedow" which has been much discussed in Europe.^{9,16}

This case is presented to emphasize the fact that the determination of plasma protein-bound iodine at one instant can reflect only the hormonal activity at that time. It can not, if normal, guarantee against future hyperthyroidism, either fresh or recrudescent. Moreover, it is not an automatic arbiter of therapeutic procedures. Indeed, in Case 91, clinically adjudged euthyroid as shown in the appended census of cases, a hyperplastic gland was found at post-mortem examination. Did premature therapy with iodine contribute to the cardiac embarrassment? Such cases as these raise

problems which suggest that smoldering or latent hyperthyroidism should be studied anew from the standpoint of therapy.

Plasma Iodine Fractions, Inorganic and Protein Bound. In Figure 3 are given data for 2 individuals, one suffering from classical myxedema and the other normal. By chance the circulating inorganic "I" iodine in the myxedema case was a little greater than the average and, on the other hand, the similar fraction for the normal individual was a little lower than the average. In consequence of these fortuitous fluctuations the total iodine value for the myxedema case was 7.1 $\mu\text{g.}$ per 100 cc. whereas the similar value for the normal individual was only 6.3. When the protein-bound "P" fractions were determined, however, that for the myxedematous patient was only 2.2, whereas the normal individual showed 4.8 $\mu\text{g.}$ per 100 cc. As explained in the preceding communication,¹ no great significance is attached to the absolute values yielded by a

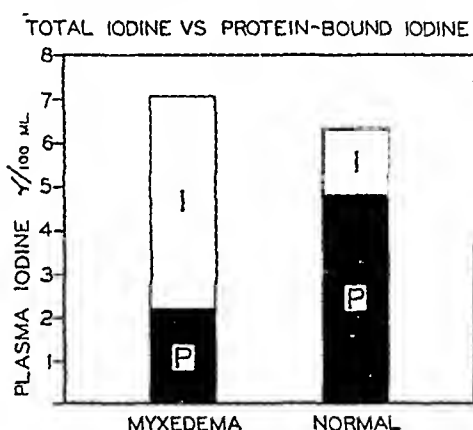


FIG. 3.—Values are given for inorganic "I" iodine and protein-bound "P" iodine in the plasma of two individuals. Obviously, unless the inorganic iodine is excluded the significant variations in "P" iodine may be masked.

partially empirical technique; the relative magnitude only is important. These two instances are cited in contrast to each other in order to illustrate why the determination of total plasma iodine may be inadequate for diagnostic purposes. This finding in part explains why, as pointed out by Greene,⁵ it has not been easy heretofore to distinguish hypothyroidism from euthyroidism on the basis of blood iodine analysis. On the other hand, all 20 of the cases of clinical hypothyroidism described in this report showed abnormally low levels for plasma protein-bound iodine.

Discussion. The data presented here indicate that when a final diagnosis of suspected thyroid disease is made in a large teaching clinic and confirmed by the determination of basal metabolic rate, the general range of plasma protein-bound iodine can be predicted with a considerable degree of certainty. In most of such cases, therefore, the analysis would be only of mild confirmatory interest.

In about one-third of the cases encountered in a large clinic, however, in which thyroid status has been suspected, the basal metabolic rate has proved not to be compatible with the best bedside diagnosis. In this second category a determination of protein-bound iodine has usually given a value confirming the clinical diagnosis and the basal metabolic rate has turned out to be misleading. In these latter cases, therefore, the determination of plasma iodine could facilitate earlier arrival at a diagnosis. This was particularly true when the elevation in basal metabolic rate was due to cardiac decompensation.

In mild hypothyroidism, before frank myxedema has developed, the finding of a low plasma protein-bound iodine has proved of considerable value in establishing the need for thyroid therapy. The application of this test is particularly desirable in younger individuals in whom the need for thyroid is more urgent and the difficulty in getting a true basal metabolic rate more apparent.

The analysis of the series of 100 test cases given here rests upon careful scrutiny of each individual case. In this respect a rather small number of cases has a distinct advantage over massed statistics in large numbers, such as have been reported in the literature. In particular, the consistency of the results here presented depends upon several factors, among which the following are especially important: 1, the utilization of plasma protein-bound iodine after excluding contact with unusual amounts of iodine, and 2, the segregation of cases of Graves' disease with hyperthyroidism from the ophthalmic cases otherwise known as "Graves' disease without hyperthyroidism." Because this segregation was made on clinical grounds, it is valid to conclude that the normal iodine values found in the plasma of these patients constitute additional evidence that Graves' disease and thyroid activity may be dissociated.¹¹ Among such patients are included former cases of chronic physiologic hyperthyroidism which are permanently or temporarily in remission, *i. e.*, the so-called "burned out" hyperthyroid patients.

In general, the clinical consistency of the data furnished by the 100 test cases and 10 euthyroid controls substantiates strongly the hypothesis raised in the previous communication¹ that plasma protein-bound iodine may be used to measure physiologic thyroid activity independently of the structural status of the thyroid gland.

Summary. A series of 100 cases of suspected thyroid disturbance and 10 control individuals has been analyzed from the standpoint of final clinical diagnosis, basal metabolic rate and plasma protein-bound iodine. When the first two of these criteria are in agreement, there is a close correlation between the plasma iodine and the basal metabolic rate. Such cases amount to 71% of the entire group studied. Of the remaining 29%, the basal metabolic rate often did not clearly reflect the clinical status and the plasma protein-bound iodine proved much more reliable. This was particularly

true in the group of "Graves' disease without hyperthyroidism" in which the basal metabolic rate ranged from -20 to $+40\%$, but the plasma protein-bound iodine was normal. These data therefore constitute additional evidence for the possible dissociation of physiologic hyperthyroidism and clinical Graves' disease. In hypothyroidism, plasma protein-bound iodine appears to be a highly reliable criterion for confirming lack of thyroid hormone, even when full-blown myxedema is absent.

It has been emphasized that the simplified chemical procedures employed are partly empirical. Their use has been justified by their consistency with clinical data, but due care should be exercised in comparing the data with the results obtained by other methods.

CENSUS OF CASES STUDIED.

Case No.	Patient.	Age.	Sex.	Hospital No.*	Diagnosis.	B.M.R.	"P" iodine, $\mu\text{g.}$
1	T. R.	44	F	979256	Myxedema	-45	2.2
2	M. H.	28	F	M.G.H. 227433	Myxedema	-43	1.9
3	N. H.	41	F	972699	Myxedema	-41	2.7
4	H. W.	42	M	970183	Postoperative myxedema	-42	3.2
5	J. O'B.	16	F	966080	Hypothyroidism	-27	2.8
6	A. McL.	55	F	999743	Myxedema	-18	0.8
7	M. B.	73	F	M.G.H. 18190	Myxedema	-50	1.6
8	A. G.	56	F	M.G.H. 270469	Hypothyroidism	-23	2.4
9	C. L.	64	F	1001923	Hypothyroidism	-18	3.2
10	M. M.	56	F	1004489	Myxedema	-28	2.2
11	M. P.	62	F	M.G.H. 263055	Hypothyroidism	-21	1.6
12	H. D.	32	F	Private	Mild hypothyroidism	-13	3.9
13	O. P.	56	F	Private	Mild hypothyroidism	-14	3.3
14	G. M.	16	F	1015066	Hypothyroidism	-20	3.6
15	G. W.	54	M	Private	Myxedema	-43	1.3
16	M. D.	33	F	M.G.H.	Myxedema	-33	2.9
17	R. J.	47	F	M.G.H. 264633	Myxedema	-32	2.2
18	H. O'N.	42	F	1026368	Pituitary necrosis with myxedema	-44	1.6
19	L. C.	71	F	1028107	Myxedema	-19	2.7
20	E. M.	45	F	M.G.H. 236576	Hypothyroidism	-34	3.4

21	G. R.	54	F	961449	Anxiety	+1	4.8
22	A. H.	46	M	Private	Tachycardia	+2	4.8
23	A. T.	29	F	1007421	Achondroplasia	+3	4.6
24	A. P.	17	F	Private	Simple goiter	-10	6.9
25	F. O.	44	F	Private	Hemangioma of skull	-1	7.4

26	J. B.	27	M	M.G.H. 263917	Graves' disease	+37	14.9
27	M. D.	25	F	970024	Graves' disease	+66	10.1
28	N. E.	49	M	992137	Graves' disease	+56	11.5
29	J. H.	69	M	988024	Graves' disease	+27	10.5

* Unless otherwise designated, the hospital number refers to cases at the Boston City Hospital.

Case No.	Patient.	Age.	Sex.	Hospital No.*	Diagnosis.	B.M.R.	"P" iodine. µg.
30	M. K.	33	F	969633	Toxic nodular goiter recurrent	+60	11.3
31	E. L.	55	F	996982	Graves' disease	+40	10.9
32	C. M.	..	F	M.G.H. 258373	Graves' disease	+41	8.3
33	D. M.	16	F	M.G.H. 231166	Graves' disease	+54	13.1
34	F. M.	31	F	976942	Graves' disease	+50	11.4
35	P. W.	39	M	963562	Graves' disease	+28	14.6
36	B. H.	18	F	M.G.H. 231737	Graves' disease	+54	13.1
37	H. Y.	54	F	993938	Recurrent Graves' disease	+32	12.1
38	H. A.	20	F	M.G.H. 274523	Graves' disease	+52	10.8
39	D. D.	19	M	977308	Graves' disease	+49	11.8
40	J. S.	51	M	969996	Graves' disease	+70	14.9
41	J. W.	59	F	973628	? Toxic adenoma	+36	11.2
42	F. L.	62	F	Evans 272458	Toxic nodular goiter	+50	16.1
43	A. B.	28	F	1004547	Recurrent Graves' disease	+33	11.7
44	M. McL.	20	F	971348	Graves' disease with thyroid storm	†	18.2
45	T. C.	24	F	1006146	Graves' disease	+64	13.5
46	A. H.	15	F	1005920	Graves' disease	+33	13.4
47	D. L.	19	F	1023229	Graves' disease	+43	18.9
48	J. S.	56	M	1007278	Graves' disease	+50	16.0
49	W. McD.	52	M	1008987	Graves' disease	+47	9.5
50	A. C.	31	M	1008240	Graves' disease	+40	24.7
51	A. G.	59	F	1011753	Graves' disease	+18	9.4
52	F. W.	61	F	M.G.H. 284938	Graves' disease	+46	8.0
53	D. B.	51	M	M.G.H. 263273	Graves' disease	+41	9.2
54	A. N.	23	F	M.G.H. 285290	Graves' disease	+51	24.2
55	B. W.	19	F	M.G.H. 285466	Graves' disease	+33	13.2
56	G. C.	42	F	1023109	Graves' disease	+30	10.7
57	G. D.	40	F	998702	Graves' disease	+40	4.9
58	A. B.	47	F	1024937	Graves' disease	+70 (±)	19.0
59	J. J.	45	M	M.G.H. 301702	Graves' disease	+18	12.4
60	C. M.	51	F	1026912	Graves' disease	+26	9.0
61	J. E.	25	F	1028809	Graves' disease	+36	8.0
62	I. B.	59	F	Private	Toxic nodular goiter	+18	9.7
63	C. M.	48	F	Westfield State Hosp.	? Cancer of thyroid	+87	13.1

64	L. C.	26	F	M.G.H. 272647	Unilateral exophthalmos	-4	6.1
65	F. L.	23	F	M.G.H. 276424	Bilateral exophthalmos	+11	7.0
66	B. H.	36	M	1017062	Bilateral exophthalmos	-10	6.4
67	M. G.	59	F	M.G.H. 280427	Bilateral exophthalmos	+8	6.7
68	A. M.	32	F	989448	Recurrent Graves' disease without hyperthyroidism	+8	6.4

* Unless otherwise designated, the hospital number refers to cases at the Boston City Hospital.

† Unobtainable.

Case No.	Patient.	Age.	Sex.	Hospital No *	Diagnosis	B.M.R.	"P" iodine. μ g.
69	S. D.	17	F	968791	Recurrent Graves' disease without hyperthyroidism	+9	7 3
70	M. K.	31	F	995785	Graves' disease without hyperthyroidism	-3	4 2
71	A. R.	22	F	1028558	Graves' disease without hyperthyroidism	+2	5 3

72	I. S.	28	F	971762	Tuberosclerosis; achondroplasia	-25	6 3
73	L. G.	43	F	976115	Intrasellar tumor	-20	5 2
74	M. S.	23	F	Private	Colloid goiter	-14	6 1
75	J. O'S.	36	M	1004320	Anxiety state	-22	5 7
76	B. M.	23	F	1002060	Hypoovarianism	-24	5 8
77	C. G.	19	F	M.G.H. 270785	Rheumatoid arthritis	-17	5 8
78	L. P.	23	F	Private	No complaint	-19	5 1
79	O. P.	28	M	Private	No complaint	-18	5 0
80	J. L.	51	M	Private	Hypopituitarism with hypogonadism	-30	4 3

81	L. S.	36	F	Private	Anxiety state, colloid goiter	+22	4 6
82	E. C.	31	F	925968	Anxiety state	+21	5 2
83	M. N.	44	F	965392	Hypertensive and arterio-sclerotic heart failure	+18	7 7
84	H. McL.	30	F	O.P.D. 613616	Anxiety, pregnancy	+29	6 6
85	C. McL.	35	F	995182	Cardiac decompensation; diffuse colloid goiter	+47	4 6
86	P. McK	52	M	967590	Hypertensive and arterio-sclerotic heart disease, decompensated	+29	4 2
87	A. S.	25	F	999787	Anxiety state	+16 to +33	5.4
88	J. D.	37	M	965164	Lobar pneumonia (fever)	+42	4 0
89	M. C.	24	F	831983	Neurosis	+47	4 9
90	F. B.	59	F	M.G.H. 297531	? Parkinson's disease; post-thyroidectomy	+29 to +50	7 1
91	B. T.	68	F	1027816	Congestive failure	+60	6 9
92	L. A.	54	F	1028709	Congestive failure	+20	6 9

93	B. B.	59	F	M.G.H. 275912	Bilateral exophthalmos	-18	4 5
94	M. F.	22	F	M.G.H. 271526	Unilateral exophthalmos	-12	4 0
95	M. C.	39	F	1028107	Bilateral exophthalmos	-20	5 3
96	H. H.	36	M	1017108	Post-thyroidectomy exophthalmos	-20	3 9
97	R. B.	22	M	1008456	Graves' disease without hyperthyroidism	-15	5 6

98	E. K.	23	F	M.G.H. 199044	Exophthalmos; ? hyperthyroidism	+17	7 1
99	M. B.	41	F	977128 990460	Graves' disease without hyperthyroidism	+36	5 5

* Unless otherwise designated, the hospital number refers to cases at the Boston City Hospital.

Case No	Patient	Age	Sex	Hospital No *	Diagnosis	B M.R	"P" iodine. μ E.
100	C. B	58	F	O P D. 662563	Recurrent Graves' disease	+14	8 8

101	S. S	26	F		No disease	0	5 1
102	J. W.	26	M		No disease	-9	5 1
103	N. S.	27	F		No disease	-4	4 6
104	M. B	29	M		No disease	-3	5 3
105	R. B.	28	M		No disease	+7	4 9
106	J. M.	27	M	982415	Acute bronchitis	-9	5 5
107	F. S	52	M	977948	Peptic ulcer	-3	5 2
108	W. B.	19	M	974372	Empyema	-9	5 9
109	L C	69	M	964840	Hypertension	-3	5 7
110	M G.	59	M	980912	Tabes dorsalis	+5	5 0

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EXPERIMENTAL ASPIRATION PNEUMONIA; FLUORESCENCE AND PATHOLOGY.†

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THE lung responds to the aspiration of foreign oils and fats by a diversity of related tissue reactions which generally are classified together, the condition being designated by a number of synonymous names, such as lipoid pneumonia, oil aspiration pneumonia, and, more recently, lipid pneumonia.* Although in routine autopsy

* Unless otherwise designated, the hospital number refers to cases at the Boston City Hospital.

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practice the origin of such lesions can often be recognized with the help of clinical information already at hand, identification of the offending substance in unknown specimens on morphologic appearances alone is difficult and often impossible.

Fluorescence of lipid pneumonia lesions in gross pathologic material has been described from this laboratory.¹³ When affected human lungs are examined under ultra-violet light in a dark room the consolidations stand out as patches of pale yellow, gray, white or greenish fluorescence. That method of examination can show up small spots of involvement which escape detection under ordinary illumination.

This study was undertaken in order to investigate further the constancy of this fluorescent phenomenon, and the relationships, if any, between substances commonly aspirated and the color tones observed. Another purpose of this paper is to elucidate in more detail than at present understood, certain variable factors as they relate to the gross and microscopic structure of lung lesions. These factors include the different foreign substances most commonly inhaled by children: cod-liver oil, mineral oil, and milk; the pathologic changes which take place with time; the differences, if any, between reactions to single and multiple inhalations; and the behavior to special staining reagents. Inasmuch as lipoid-containing cells have been repeatedly described in milk aspiration pneumonias, a series of observations on aspiration pneumonia due to butter fat and milk free from fat have been included.

The literature on this condition is increasing rapidly, mainly because of the growing alertness of clinicians and radiologists to its occurrence. The most common offenders in humans are considered to be mineral oil, plain or medicated, cod-liver oil, castor oil, olive oil, and the butter fat of milk formulas. Their entry is usually by way of oily nose drops or by choking upon or swallowing improperly oily or fat-containing substances.

As recorded in the literature the gross appearance of affected human lungs is variable. The involved portions may be pale yellow, gray-white, or gray; large or small; sharply margined or with indefinite borders; scattered or clumped. Accompanying bronchopneumonia usually obscures the specific consolidation. An oily appearance is given only by freshly aspirated material. The distribution of the lesions demonstrates the exogenous entry of the contained fat or oil, inasmuch as the posterior and inferior regions and the perihilar areas are most often affected, and the right lung usually is involved more extensively than the left.³

The microscopic reactions have also been described in great detail, and can be summarized as follows: The picture varies with the kind and amount of the aspirated lipids, the age of the lesions, and the character and extent of the complicating secondary pneumonia so frequently present. Oil globules may lie free in the alveolar

spaces or be encysted within mononuclear foreign body giant cells. Neutrophils are not present in any number except when the oil contains fatty acids or other irritant substances, or if bacterial invasion has taken place. Large macrophages take up and hold the oil droplets; at times these phagocytes coalesce to form giant cells of the foreign body type. The alveolar lining may take on a cuboidal or columnar shape when stimulated by medicament-containing mineral oil or by cod-liver oil. Following entry of irritating oils the immediate response is local hemorrhage and edema, fatal if the inflammation is sufficiently great. When bacteria in any abundance are present within the foreign material the inflammatory reactions become much more violent and can go on to abscess formation. The end-result of lipid aspiration is usually residual fibrosis with giant cell formation, round cell infiltration and granulomatous nodules. Much of the oil is disposed of through expectoration, some is destroyed *in situ*, some is carried off into the lymphatics, while the residue, of variable quantity, remains locally in granulomas within the lung.

A number of practical suggestions for use in identifying the various oils have been suggested, based on differences in the histologic architecture and staining responses of lesions in experimental and clinical material. Cod-liver oil, chaulmoogra oil, and lard are highly irritating, presumably because of their highly unsaturated fatty acids, whereas olive oil, sesame oil, and cottonseed oil are much more bland. Mineral oil, a hydrocarbon, is freely phagocytosed by macrophages and remains as a persistent inert foreign body encapsulated in fibrous granulomas, although when drugs such as ephedrine or camphor are contained in it the pulmonary reactions become more extensive.⁸ Cod-liver oil gives rise to an acidophilic hyaline membrane which is acid-fast to carbol fuchsin as used in the staining of tubercle bacilli;^{7,11b} this membrane persists for a long time, ultimately becoming phagocytosed. Confirming data can sometimes be obtained by chemical studies of the involved tissues.

Yet, in spite of the mass of observations on record, all details of the pathologic change have not been fully elucidated, especially with regard to the comparative importance of milk and milk products in the pathogenesis of the disorder.

Method. The foreign substances utilized in this study were as follows: 1, Cod-liver oil (U.S.P.); 2, mineral oil (U.S.P.); 3, canned evaporated milk diluted with equal parts of sterile distilled water; 4, fresh unsalted melted butter (not autoclaved), and 5, centrifuged autoclaved market milk containing less than 0.01% butter fat.

The experimental animals were young healthy New Zealand Red rabbits at sexual maturity. Though previously used in Friedman pregnancy tests, they had been given a 2- to 4-week recovery period and were free from snuffles and wound infections. Their weight ranged between 4 and 5½ lbs. at the onset of the observation period, and between 5 and 10 lbs. at the time

of killing. Five groups of such rabbits, 21 to 24 in each group, were taken. As controls, the lungs of some 20 uninoculated animals of comparable condition were studied in exactly similar fashion.

To simplify the comparisons all substances were instilled under essentially identical circumstances in accordance with the same fixed schedule. One to five instillations were given, spaced from 1 to 7 days apart. The oils were dropped into each nostril in 1 cc. doses; the milk preparations, warmed, in 5 cc. quantities.

The animals, lightly anesthetized with ether, were held vertically during the instillations. They were killed at progressive intervals of from 2 days to 1 year following the final treatment, by means of intravenous injections of air. Immediately afterwards the lungs were removed, and their gross appearances noted in ordinary light and under the fluorescent lamp. Ten per cent formalin solution was used as the hardening and preserving fluid. The ultra-violet ray observations were repeated several times later in order to determine the effects, if any, of this fixing fluid on the fluorescence phenomenon.

Paraffin sections made from grossly consolidated areas were stained with hematoxylin and eosin, and also with the acid carbol-fuchsin stain. Scarlet red staining of frozen sections was used for recognizing the fat globules. A fourth set of frozen sections have been mounted in water glass upon special ultra-violet transmitting glass slides and set aside for future study with the ultra-violet microscope.

The specimens were studied for the following points: gross appearances of the consolidated areas as seen by the naked eye and under the fluorescent lamp; histologic cellular reactions as related to offending foreign substances and to the intervals since the final inhalations; extent of the inflammatory response in comparison with the amount of foreign material demonstrable; length of time necessary for complete disappearance of the aspirated material; and subsequent presence or absence of residual alterations in the cellular architecture of the lung tissue.

Observations. *Distribution of the Lesions.*—The distribution of the foreign materials and of the pneumonic reactions to them proved to be more or less the same with all substances tested. The lesions were scattered unevenly through all parts of the lungs, usually being larger and more abundant in the lower lobes, presumably because of the upright position of the animals during the instillations. All parts of the lobes were involved, without noticeable selective localizations in the hilar regions. Subpleural lesions could be easily recognized on inspection. Wide fluctuations in size and distribution of the pneumonic patches were observed with each of the substances; some pairs of lungs being flooded with specific consolidations whereas others displayed only a few isolated spots. Clearly the quantities of instilled liquid which passed the laryngeal barrier were inconstant and unequal, in spite of every attempt to keep the experimental conditions constant.

Fluorescence. For the purpose of detecting fluorescence in lung specimens simple dark lamps such as geologists use were found suitable. With the shorter ultra-violet wave lengths (2400–2800 a.u.) the lung tissue emitted a dark red glow due to the hemoglobin, which persisted to obscure the colors of the pneumonic areas even after prolonged formalinization. But under the longer ultra-violet

waves (2800–3100 a.u.) the hemoglobin fluorescence of the background of lung tissue became practically invisible after a few days' contact with formaldehyde.

The fluorescence of the aspiration pneumonias usually grew more prominent when the tissues had been preserved for several months. This technique of repeated observation proved helpful in uncovering small patches of aspiration pneumonia not detectable under ordinary illumination.

Multiple Instillations. In the animals which had received multiple instillations over periods of several days the sections showed the changes of early acute inflammation phenomena side by side with more advanced subacute reactions.

Cod-liver Oil. The pneumonic patches looked yellow or yellow-brown in both fresh and formalinized specimens. Of all the experimentally produced aspiration lesions those of cod-liver oil were the largest, especially in their early stages when many possessed central foci of liquefaction. Under ultra-violet light the patches fluoresced brightly, showing color effects noted as yellow, pale yellow, cream, or yellow-brown.

Histologic changes bore a constant relation to the age of the lesions. In the youngest preparations (2 to 4 days) amorphous eosinophilic extracellular masses of oil surrounded by large numbers of phagocytes, neutrophils, eosinophils and monocytes were scattered through alveoli and bronchioles. Within the larger lesions central liquefaction soon occurred (4 to 7 days). Later on (7 to 10 days) the cells lining the alveoli sometimes swelled and became cuboidal; the neutrophils became less plentiful (Fig. 1). Most of the phagocytes were monocytes and eosinophils, with fibroblasts beginning to make an appearance. The amorphous deposits had become smaller and were being penetrated by the leukocytes. After 15 days, inflammatory granulation tissue encapsulated the oily debris and the abscesses had disappeared. Scar tissue and foreign body giant cells were replacing the earlier acute exudate. Even after 1 year these granulomas of giant cells, eosinophils, and fibrous tissue surrounding hyaline yellow-colored foreign material were still prominent (Fig. 2).

Scarlet red preparations showed an abundance of orange-red staining fatty material at all times. After the first few days the larger deposits were shown contained within syncytial cell masses, while the small drops were engulfed by individual lipophagic monocytes. Even after 2 months not much fine emulsification had taken place, though there was a definite trend toward reduction in droplet size with the advance of healing.

In the sections stained with carbol fuchsin the lipid material appeared as acid-fast droplets, both intracellular and extracellular. The intensity of staining fluctuated somewhat among the various specimens, and was not striking in the more advanced lesions. In

the freshest lesions staining was deepest at the periphery of the oily masses.

Mineral Oil. In freshly removed lungs the affected areas appeared gray-white and bloodless, easily visible against the pink spongy

FIG. 1.

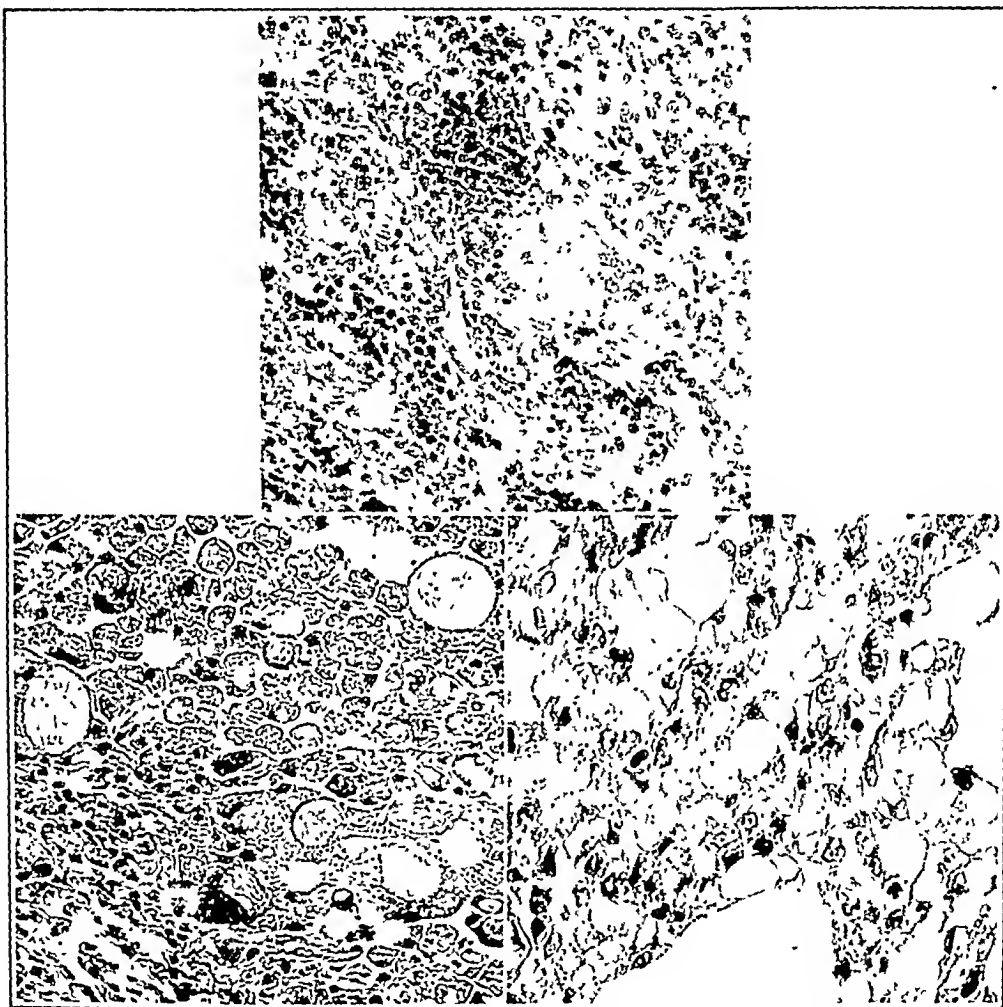


FIG. 2.

FIG. 3.

FIG. 1.—Lung, 10 days after single inhalation of cod-liver oil. ($\times 400$.) Lipid material is seen within a large multinucleated foreign body giant cell. A cluster of leukocytes, consisting chiefly of neutrophils, lies in close proximity. The neighboring mononuclears contain small droplets of oil.

The defects in these photomicrographs are in the original slides and not in the photographs or their reproduction.

FIG. 2.—Lung, 8 months after 3 inhalations at weekly intervals of cod-liver oil. ($\times 400$.) Granular deposits of pale yellow lipid remain within large mononuclears and giant cells. Evidences of acute irritation are not present. An almost identical appearance was observed in the 12 months' specimen.

FIG. 3.—Lung, 15 days after single inhalation of mineral oil. ($\times 500$.) Oil globules of varying sizes lie within the alveoli, either phagocytosed by single cells or surrounded by syncytial masses. No oil lies free in the alveolar spaces. The deeply staining small phagocytes are eosinophils. Neutrophils are rarely seen.

parenchyma of the surrounding lung tissue. After formalin fixation they were much less prominent, though always whiter than the pulmonary tissue background. Under the ultra-violet lamp they were manifest as pale gray spots tinted at times with an added faint green, green-blue, or blue color.

In the early stages (Fig. 3) the affected alveoli and terminal bronchioles were packed with a syncytial-like mass of phagocytes having cytoplasm filled with large and medium-sized vacuoles. In specimens but 2 days old many oil drops appeared to be large and extracellular, but after a few days they had become broken up, giving to the cross-section a foamy pattern. After some months, however (Fig. 4), a marked tendency to fine emulsification had become evident. With the passage of time the lining cells of the involved alveoli took on a cuboidal shape, their walls became thickened, and some vacuolated macrophages became deposited in the interstitial connective tissue. The only other tissue response was the appearance of eosinophils in small numbers in some specimens.

In 2 of the animals which had received multiple instillations patches of necrosis, hemorrhage and acute inflammatory reaction were discovered, but the presence of large colonies of bacteria in the Gram-stained preparation indicated the existence of a superimposed acute bacterial pneumonia.

With scarlet red the color assumed was orange yellow, much paler than that given by the cod-liver oil and butter fat preparations. Mineral oil did not stain with carbol fuchsin.

Evaporated Milk. Fresh lungs removed during the first 2 weeks following instillation of milk showed gray-white pneumonic mottling which remained paler than the surrounding tissue after fixation in formalin. Under ultra-violet light the pneumonia had a white color, better shown in the formalinized material. With ordinary illumination no consolidations were recognizable later than 2 weeks, although small fluorescent white spots persisted up to 30 days of age.

Within 2 days after inhalation the microscopic examination showed a pneumonic reaction so extensive that the contours of the alveolar network were completely obscured (Fig. 5). One saw a solid mass of fibrin, mononuclears, neutrophils, eosinophilic cells and fibrous tissue homogeneously commingled with some finely granular purple staining debris. Vacuolated monocytes were uncommon. After a few days the picture had not altered much except for diminution in the proportion of neutrophilic cells. Abscesses did not form. At one week the amorphous material could no longer be seen, and by 2 weeks the reactions had largely subsided, leaving small areas of scarred thick-walled alveoli, containing a few monocytes of irregular shape. At 1 month and later the lungs seemed completely recovered except for residual alveolar thickenings, apparently permanent, and a few eosinophilic cells seen here and there. At no time did the alveolar epithelium itself assume a cuboidal form.

In the scarlet red preparations, occasional monocytes filled with fine red globules were seen in small groups within the acute inflammatory exudate. These cells decreased in numbers during the

FIG. 4.

FIG. 5.

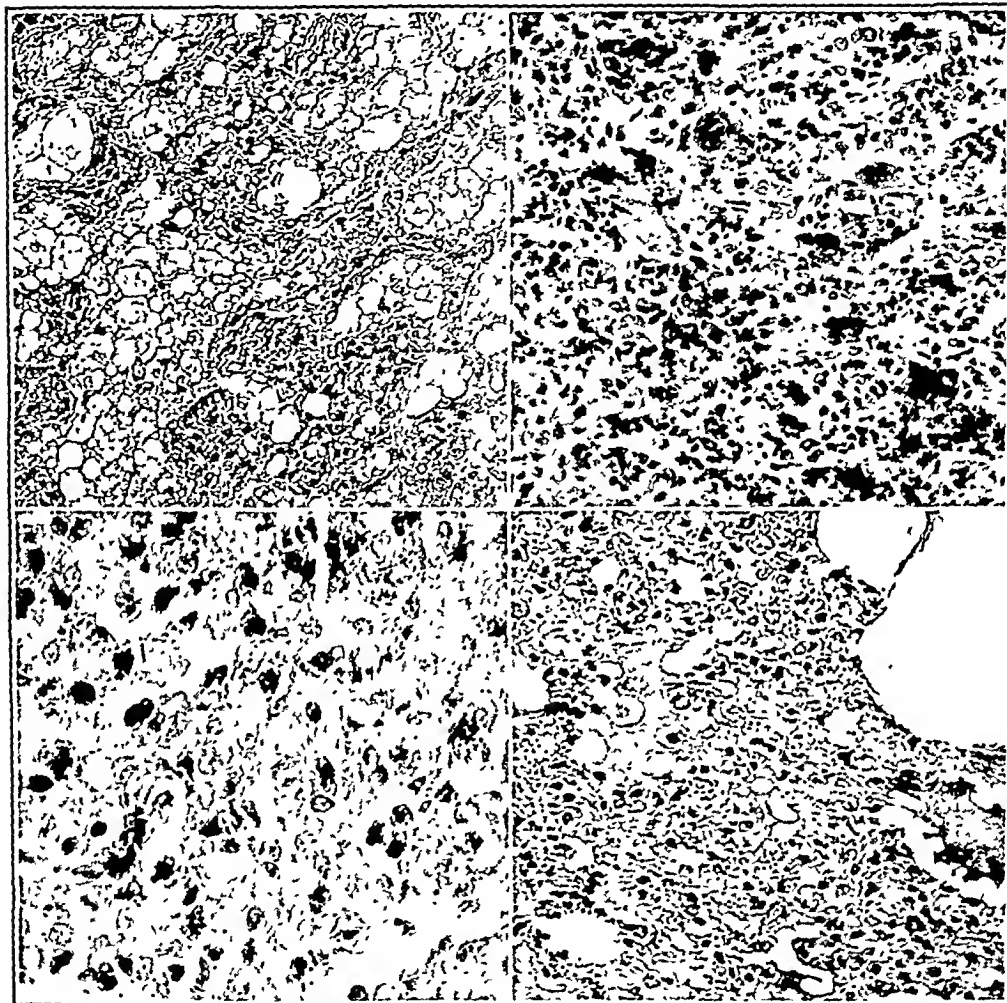


FIG. 6.

FIG. 7.

FIG. 4.—Lung, 8 months after 3 inhalations at weekly intervals of mineral oil. ($\times 210$.) Masses of vacuolated mononuclear cells containing large and small globules fill the alveoli. The alveolar walls are thickened and fibrosed. An almost identical appearance was observed in the 12 months' specimen. The deeply staining cells are eosinophils.

FIG. 5.—Lung, 2 days after single inhalation of evaporated milk. ($\times 400$.) The alveoli are jammed with an intense inflammatory exudate consisting of neutrophils, edema fluid, basophilic coagulum, and mononuclear phagocytes.

FIG. 6.—Lung, 2 days after single inhalation of fat-free cow's milk, boiled. ($\times 566$.) The exudate is less intense than with whole milk, neutrophils are less abundant, and basophilic debris is difficult to identify.

FIG. 7.—Lung, 2 days after single inhalation of melted butter. ($\times 300$.) Butter, which stains deeply eosinophilic, is quickly liquefied. Note the mononuclear cells lying within lacunar pockets along the margins of the drops. The cellular response consists almost entirely of monocytes and eosinophils.

stage of resolution, and could not be found after 3 weeks. The carbol-fuchsin preparations were negative for the presence of oil residue.

Butter. In recently affected lungs the patches of consolidation were dark gray in color, more easily identified in the unpreserved specimen than after fixation. In the 1- and 2-month-old specimens no lesions could be seen. Under ultra-violet light the fluorescent effect was given by some but not all of the very early lesions, the color being faint gray-white tinged with green. In older inflammations the color was an indefinite white or gray and frequently could not be detected at all. Immersion in formalin intensified this white color; with some specimens recognition of the lesions in fresh tissue was difficult or impossible, but fluorescence studies subsequent to fixation demonstrated the involved areas.

On microscopic examination the immediate reaction to butter fat was found to consist of a patchy inflammatory exudate containing many monocytes, some neutrophils, and an occasional eosinophilic cell. The lipid material formed eosinophilic amorphous masses with scalloped margins (Fig. 6). Abscess formation did not occur and there were no acute inflammatory reactions which might be interpreted as a response to the bacteria present in butter. By the end of the week the picture was little altered except for the disappearance of the extracellular lipid. During the following week or two most of the reaction had faded away, but at 1 month and occasionally later one could find clusters of pigmented brown non-vacuolated irregular monocytes scattered among the alveoli.

With scarlet red, the butter stained vividly. After the first few days the butter fat had been completely phagocytosed and appeared as large intracellular globules. In time these globules multiplied and grew smaller, so that by 2 weeks they gave a stippled appearance to the cytoplasm. After 15 days prolonged search of the sections was needed to find a few cells having small intracellular fat globules; after 30 days none could be found. Carbol-fuchsin stains of the pneumonia area were negative for acid-fast matter.

Autoclaved Fat-free Milk. (This milk was sterilized and cooked by autoclaving for 30 minutes at 240 lbs. pressure and 115° C. temperature after being skimmed by high speed centrifugation. Fat content less than 0.01%.) The gross and fluorescent appearances of the pneumonia were identical with those of sterile evaporated milk. No fluorescent lesions could be found after 30 days.

In the paraffin sections the acute inflammatory reaction was similar to but not as violent as that observed with evaporated milk (Fig. 7). The exudate consisted largely of mononuclear cells. Débris and neutrophils were much less plentiful whereas the eosinophils were fairly numerous. By 10 days the neutrophils and débris had steadily receded and faded away and only foci of monocytic infiltration remained. At 1 month and later one saw only occasional thickened alveolar septa.

TABLE 1.—DIFFERENTIAL CHARACTERISTICS OF ASPIRATION PNEUMONIAS.

	Distribution of lesions.	Observed duration of lesions.	Color of gross lesions.	Central liquefaction at onset.	Ultra-violet fluorescence.		Intensity of acute inflammation in early stages.	Scarlet red stain.	Carbol fuchsin stain.	Fat particle size.	
					Recent aspiration.	Older lesions.				Recent aspiration.	Older lesions.
Cod-liver oil	All lobes, esp. in dependent regions	At least 1 yr.	Yellow or yellow-brown	++	Yellow	Pale yellow	++++	Orange-red	+	Large, irregular	Large and small
Mineral oil	All lobes, esp. in dependent regions	At least 1 yr.	Pale gray or white	0	White	Gray-white	++	Yellow	0	All sizes, rounded	Small
Evaporated milk*	All lobes, esp. in dependent regions	1 mo.	Gray-white	0	White	0	++++	Scarlet	0	Fine (rare)	0
Butter	All lobes, esp. in dependent regions	1 mo.	Dark gray	0	Gray-white with green tint	0	++	Scarlet	0	Large	Finely stippled
Autoclaved fat-free milk	All lobes, esp. in dependent regions	1 mo	Gray-white	0	White	0	+++	0	0	0	0

* Water added

No signs of fat infiltration were found in any of the frozen section preparations except for a few rare clusters of finely stippled macrophages in some of the animals which had been given multiple inhalations. The carbol-fuchsin preparations failed to reveal acid-fast matter.

Comment. The data presented show that under the conditions of the experiments the pathologic reactions produced by the different substances tested were individually characteristic (Table 1). Cod-liver oil provoked a violent necrotizing reaction which partially cleared to leave chronic granulomatous deposits. It was the only lipid in this series to possess acid-fast staining properties with carbol fuchsin. Mineral oil produced little acute inflammation and remained indefinitely as an unabsorbable foreign material. Butter fat gave rise to an immediate mononuclear response of transitory character. Evaporated milk stirred up a distinctive inflammatory reaction, also transient, in which the presence of small numbers of phagocytes holding fat could be considered as being entirely a response to its contained butter, inasmuch as no lipophages were found in the similar though milder experimental lesions produced with autoclaved fat-free milk. With the scarlet red stain butter fat appeared dark red, cod-liver oil was orange-red, and mineral oil orange-yellow, demonstrating decreasing rates of solubility in the order named. Under ultra-violet light the various pneumonias presented differing and individually typical color fluorescence. Further investigation has brought out that the fluorescent effects of these pneumonias are essentially the same as the colors given by the foreign materials themselves when examined in the pure state under ultra-violet light.

The effects of repeated inhalations were not strikingly dissimilar from those following single inhalations. Where the pathologic appearances changed quickly with progress of time the examinations showed lesions of various ages existing side by side. When the tempo of reactive change was more slow-paced it was impossible to distinguish between the lesions of single and multiple instillations.

The morphologic changes following milk aspiration, whether of normal fat content or fat-free, were of a character most unlike those of the oils and fats studied. There were no lipid deposits and the feature of chronicity was lacking. The pulmonary reactions were found due to irritation from the contained butter fat as well as from other components of the milk. If the designation "lipid pneumonia" persists in general use the milk aspiration lesions ought not to be included.

The observations reported here were restricted to rabbit lungs, but the findings are sufficiently clear-cut and distinctive to warrant the presumption that they parallel in general contour the pictures encountered in affected human necropsy material.

Conclusions. 1. The pathologic reactions in rabbit lungs to the introduction of cod-liver oil, mineral oil, butter, evaporated milk, and autoclaved fat-free milk have been studied.

2. Each of these foreign substances gave rise to characteristic changes sufficiently distinctive as regards gross appearances, histologic architecture, staining reactions, and fluorescent behavior to permit accurate identification, not only of the foreign substance itself, but often, also, of the age of the lesion.

3. The pathologist when studying autopsies should attempt to make specific diagnoses such as mineral oil pneumonia, cod-liver oil pneumonia, and milk aspiration pneumonia, rather than be satisfied with the less definitive terms aspiration pneumonia or lipid pneumonia.

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THE ACTION OF GLOBIN INSULIN COMPARED WITH THAT OF CRYSTALLINE, UNMODIFIED, AND PROTAMINE ZINC INSULIN.

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AN important aim in the treatment of diabetes mellitus with insulin is to give a sufficient quantity in one injection in conjunction with an adequate diet to maintain the level of the blood sugar within the limits of normal for a period of 24 hours. This is not possible, in the majority of patients, with any one of the insulins commercially available; namely, unmodified, zinc insulin crystals in solution (crystalline insulin) and protamine zinc insulin. The action of unmodified and crystalline insulin upon the blood sugar concentration occurs promptly and subsides within 6 to 10 hours after they are injected subcutaneously. Protamine zinc insulin is slow to act but its action persists from 24 to 36 hours after administration. Hence, in most cases, a single dose of any one of these three brands

of insulin causes a blood sugar lowering action which is either too rapid and too evanescent or too gradual for the satisfactory control of the diabetes. Satisfactory results are secured by combining these effects with the separate injection of two insulins, a rapidly acting and a slowly acting insulin.* This entails 2 or even 3 injections a day for the patient having severe diabetes.

To obtain satisfactory control of the diabetes by a single daily injection of insulin it would appear that for the majority of patients it would be essential to have an insulin which acts with sufficient rapidity to prevent hyperglycemia during the daytime, when three meals are taken in close succession, and with an action sufficiently prolonged to control the level of the blood sugar throughout the night. In this manner the shortcomings of the protamine zinc insulin and the crystalline insulin in the routine treatment of many patients who require insulin would be overcome.

There is evidence that globin insulin fulfills this purpose and affords certain other advantages. Bauman² in the first report on the clinical use of globin insulin found: 1, that its maximum hypoglycemic effect occurred about 8 hours after its injection, and that if too much was given before breakfast hypoglycemic reactions would occur in the late afternoon; 2, that a single dose of globin insulin controlled mild and moderately severe diabetes for a 24-hour period; 3, local allergic reactions at the site of injection were promptly relieved when globin insulin was substituted for protamine zinc insulin. Marks⁵ has found that globin insulin "acts more strongly than protamine upon the breakfast carbohydrate and completes its action during the night with no perceptible carry-over." Andrews and his associates¹ found that fewer units of globin insulin were necessary to control hyperglycemia than when protamine zinc insulin was used. A single dose of globin insulin controlled severe cases of diabetes even when this end had not been accomplished with the combined use of crystalline and protamine zinc insulin. No nocturnal hypoglycemic reactions were observed when only one daily dose of globin insulin was employed. The maximum effect from globin insulin was manifested at approximately 8 hours after its injection and its effect became exhausted in about 15 hours.

The object of this investigation was to observe, under exactly controlled conditions, the effects of globin insulin as compared with the insulins now commercially available.

The globin fraction of globin insulin is prepared from beef blood, although it may be prepared from the blood of other animals, or from human blood. Globin is a simple protein which is soluble at its iso-electric point. It is obtained by removing the iron-containing chromogen fraction from the hemoglobin molecule. Globin does not yield histopeptone on hydrolysis, and therefore should not be

* Some authorities mix the rapidly and slowly acting insulins in the syringe and inject them simultaneously. This technique has been unsatisfactory in our hands.

classified as a histone.⁴ The globin insulin used in this study was prepared in the Experimental Research Laboratories of Burroughs, Wellcome and Company. It contains 3.04 mg. of globin, 0.24 mg. of zinc, and 80 units of insulin per cc.⁶ It is a clear, yellowish fluid having a pH of 3.7.

Methods.—Before attempting the routine treatment of diabetic patients with globin insulin it seemed advisable to determine the time of onset, the intensity, and the duration of the hypoglycemic effect produced by a single injection of this product and to compare the results with those produced by single doses of the types of insulin now in common use.

Forty-two patients from the medical wards were studied during this investigation; the results observed in 5 patients, each representative of a similar group, are reported in detail. They are: a non-diabetic adult (T.B.), an elderly man with very mild diabetes (A.Z.), a middle-aged man with mild diabetes (J.J.), a slender middle-aged man with severe diabetes (D.C.), and a young man of 18 years having very severe diabetes (H.M.). All of the patients were in the hospital for the duration of the study. During this period they were given weighed diets appropriate for their metabolic needs. Those who required insulin received their usual daily dose between the periods of observation. In order that the results might not be confused by the presence of insulin which was not yet absorbed and utilized, the subjects received no insulin for at least the 36 hours preceding the injection of the test doses. They received their usual meals during this period. The amount of insulin in the test dose given to each subject was determined on the basis of the severity of the diabetes as judged by his age, body weight, and the amount of insulin previously required. Upon the day of the test the insulin was given after venous blood had been obtained for determination of the fasting blood sugar level.* To maintain a uniform intake of carbohydrate throughout the period of observation, fruit juice, containing 20 gm. of carbohydrate, was given to each subject at the time of the administration of the insulin and at intervals of 2 hours thereafter until the conclusion of the test. Determinations of the blood sugar level were also made at intervals of 2 hours. In almost all instances the observations were continued until the blood sugar values had risen from the hypoglycemic values to the original fasting levels. The observations were repeated at intervals of at least 1 week until all three insulins were tested.

Case Reports. CASE 1.—T.B., a white male, aged 47, height 172.7 cm. (68 inches), weight 70.8 kg. (156 pounds), was admitted on December 22, 1939, because of vomiting and a history of "tarry stools." Studies failed to reveal any pathologic change in the gastro-intestinal tract. There was no evidence of diabetes mellitus. He was given a diet containing protein 70 gm., carbohydrate 175 gm., and fat 83 gm. (1750 calories). No insulin was given except upon the days selected for the tests. The dose of insulin selected for this patient was 15 units, as this was considered sufficient to give a moderate degree of hypoglycemia without producing unconsciousness. The fasting blood sugar concentration varied between 84 and 100 mg. per 100 cc. Following the separate administration of unmodified and of crystalline insulin there was in each instance a reduction in the blood sugar level within 4 hours to a level of 76 and 49 mg. per 100 cc., respectively. The fasting level was restored within 10 hours after the injection in both instances. When protamine zinc insulin was given, the blood sugar level fell very slowly from a fasting level of 97 mg., reaching 77 mg. per 100 cc. in 10 hours and maintaining a low level for 21 hours. When globin insulin,

* Determinations of the blood sugar level were made using Benedict's modification of the micro-method of Folin and Wu.

15 units, was given, the blood sugar level fell from a fasting value of 100 mg. to 78 mg. per 100 cc. in 4 hours. The blood sugar concentration remained fairly constant about this level until 20 hours had elapsed. The fasting level was restored by the end of 22 hours (see Chart 1).

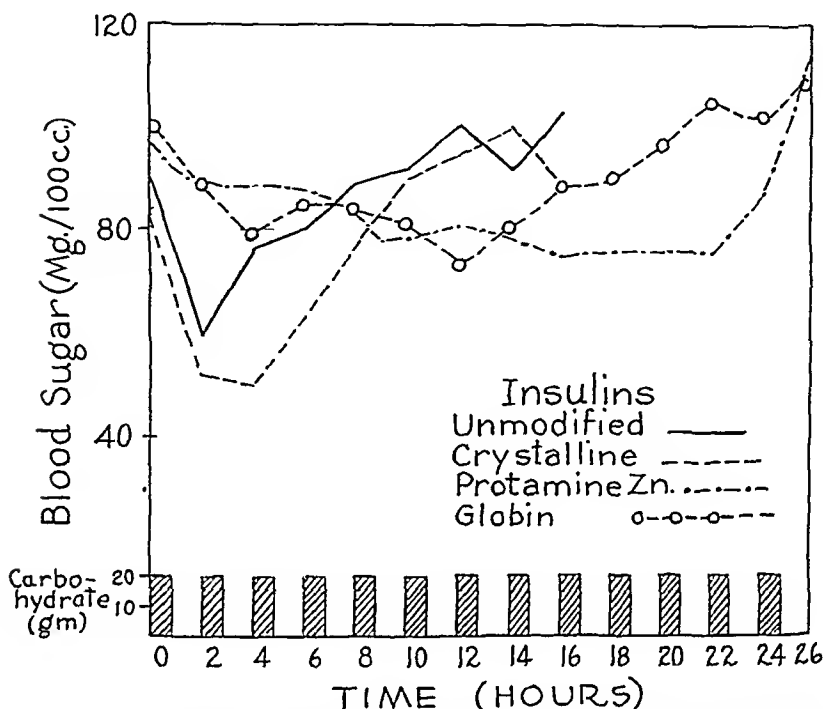


CHART 1.—Case 1 (T.B.). Globin insulin (15 units) has a more prompt but not as prolonged hypoglycemic action as protamine zinc insulin, and a more gradual and more prolonged action than the same doses of crystalline and unmodified insulins.

Comment. There is a contrast in this non-diabetic subject between the effects of 15 units of unmodified and of crystalline insulin, both of which had a rapid but evanescent action, and protamine zinc insulin, which had a retarded and prolonged action. The action of globin insulin like that of unmodified and crystalline insulin began soon after its injection but was continued for a much longer time than was the case with either of these insulins. This prolongation of action is, however, slightly less than that observed with protamine zinc insulin.

CASE 2.—A.Z., a white male, aged 62, height 165.7 cm. (66 inches), weight 61.2 kg. (135 pounds), was admitted on September 8, 1939. He had a history of diabetes mellitus of 9 years' duration. This patient had never required insulin and he was free from glycosuria when the diet contained protein 80 gm., fat 68 gm., and carbohydrate 140 gm. (1500 calories). For the purposes of this study 30 units of each of the insulin preparations were employed. Unmodified insulin reduced the blood sugar level from 90 to 51 mg. per 100 cc. during the first 4 hours. The blood sugar returned to the fasting level by the 14th hour. A similar, but more rapid reduction in the

blood sugar concentration was observed after the administration of crystalline insulin. Protamine zinc insulin reduced the blood sugar level, particularly after 4 hours, to reach a minimum of 53 mg. per 100 cc. in 18 hours. The fasting value was not regained in 28 hours. When globin insulin was given, the blood sugar values rose during the first 4 hours from 91 to 114 mg. per 100 cc., after which a prompt reduction ensued. The fasting level was not regained until the 32nd hour (see Chart 2).

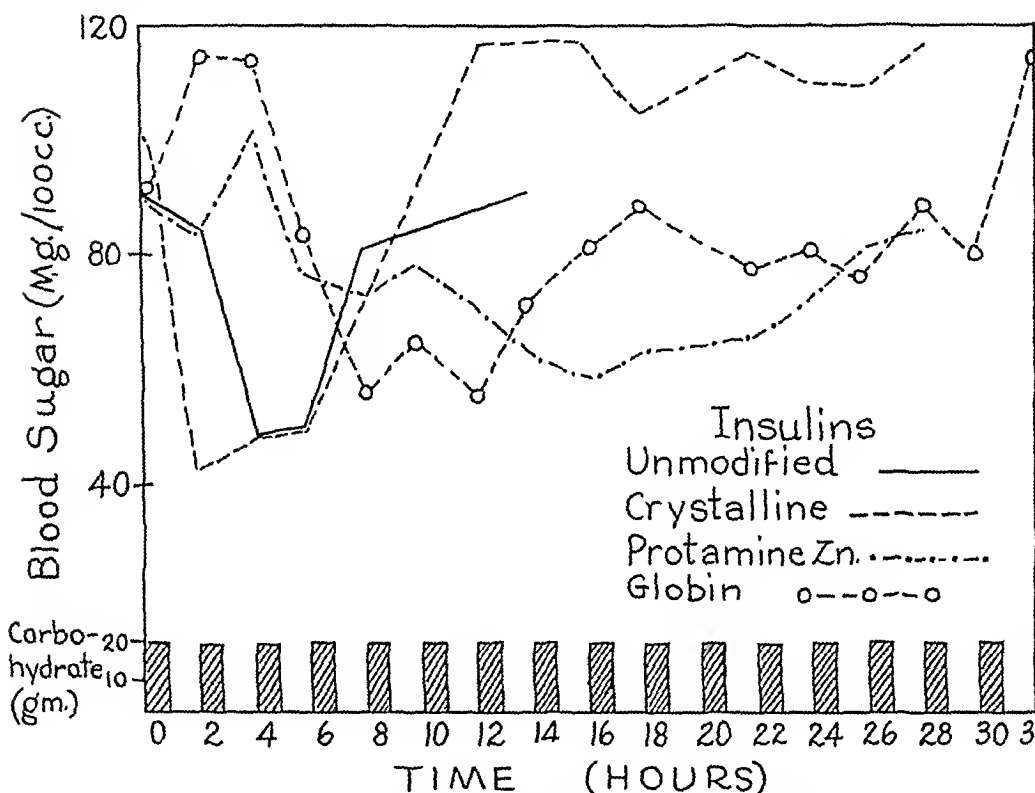


CHART 2.—Case 2 (A.Z.). Globin insulin (30 units) has the same intermediate effect as in Chart 1.

Comment. Unmodified and crystalline insulin each caused a prompt but fleeting reduction of the blood sugar level. Protamine zinc insulin exerted a gradual but prolonged blood sugar lowering effect. The effect of globin insulin fell between that of the rapidly and slowly acting insulins. It reduced the blood sugar level more quickly than did the protamine zinc insulin and more slowly than did the crystalline insulin. Its effect persisted longer than that of crystalline insulin and yet not as long as that of the protamine zinc insulin.

CASE 3.—J.J., a colored male, aged 56, height 173.9 cm. (68½ inches), weight 76.2 kg. (168 pounds), was admitted on January 9, 1940. His diabetes was of 2 years' duration. On a previous admission he received a diet containing protein 72 gm., fat 132 gm., and carbohydrate 132 gm. (2000 calories) and 48 units of protamine zinc insulin, and 18 units of unmodified insulin before breakfast each morning. During this investigation the same diet was prescribed. On successive weeks he was given a

test dose of 48 units of globin, protamine zinc and crystalline insulin respectively. Globin insulin promptly reduced the blood sugar concentration from 154 mg. to 50 mg. per 100 cc. during the first 6 hours following which the blood sugar concentration rose gradually to exceed the original fasting level at the 24th hour (see Chart 3). After the administration of protamine zinc insulin the blood sugar level rose slightly from 140 to 145 mg., in the first 2 hours and then fell gradually to levels between 97 and 137 mg. per 100 cc. which were maintained until the conclusion of the period of observation 28 hours after administration. Prior to giving 48 units of crystalline insulin, the fasting value of the blood sugar was 121 mg. per 100 cc.; the level rapidly fell to 35 mg. in the first 2 hours after the insulin was given and then it gradually rose to levels above the fasting value at the 22nd hour.

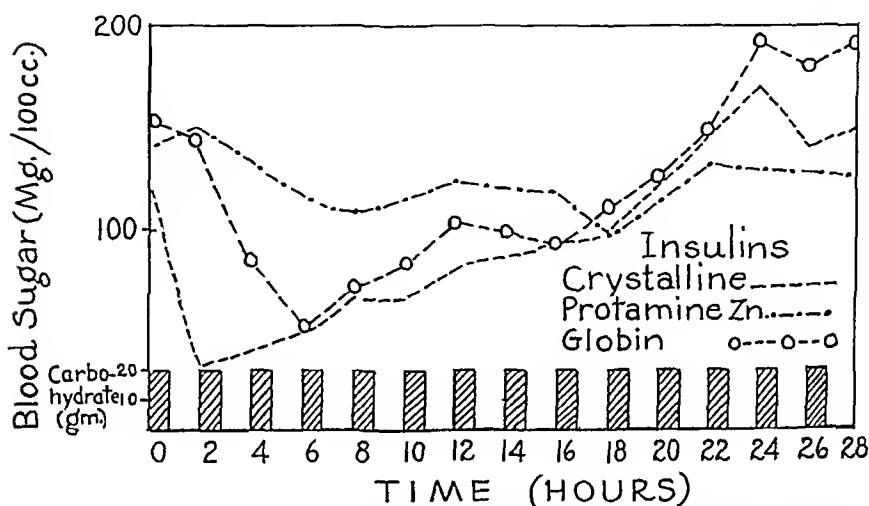


CHART 3.—Case 3 (J.J.). The intermediate effects of 48 units of globin insulin are depicted. The mildness of the diabetes prevents making conclusions concerning the duration of the effects of the respective insulins.

Comment. The immediate hypoglycemic response following the injection of crystalline insulin is in contrast with the slightly slower response to globin insulin and the very gradual lowering of the blood sugar level after protamine zinc insulin was given. The similarity of the curves obtained from plotting the blood sugar values obtained between the 6th and 24th hours following the injection of crystalline and globin insulin is a phenomenon often observed in patients who have a mild diabetes in whom the onset of insulin action is evident but in whom it may be impossible to tell when it ends. In these patients the blood sugar level may not rise promptly when the insulin action is exhausted.

CASE 4.—D.C., a white male, aged 55, height 162.5 cm. (64 inches), weight 61.2 kg. (135 pounds), was admitted on August 28, 1939, with a history of having had diabetes approximately 2 years. A diet containing protein 70 gm., fat 116 gm., and carbohydrate 200 gm. (2200 calories) was prescribed. The test dose of 78 units of unmodified insulin reduced the blood sugar level from a fasting value of 180 mg. to 41 mg. per 100 cc.

during the first 4 hours after which it rose, reaching 216 mg. 12 hours after the injection. After 78 units of protamine zinc insulin were given there was a rise in the blood sugar level from 183 mg. to 209 mg. per 100 cc. during the first 4 hours and then a reduction ensued and values within the limits of normal were maintained from the 10th to the 26th hour. The same amount of globin insulin (78 units) caused the blood sugar level to fall from a fasting level of 214 mg. to 58 mg. during the first 2 hours, to 38 mg. per 100 cc. in the next 2 hours. Subsequently, the values increased slowly until the 18th hour, after which it quickly rose to the fasting level (see Chart 4).

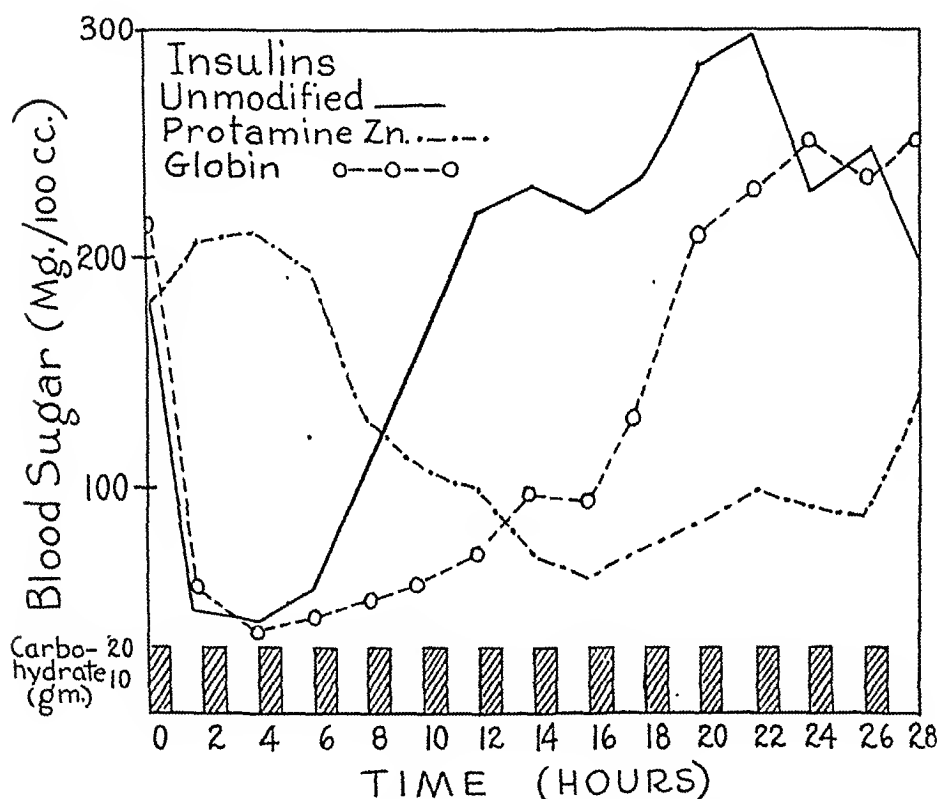


CHART 4.—Case 4 (D.C.). The speed with which the blood sugar levels were reduced and the duration of the hypoglycemic effects of 78 units each of globin, crystalline and protamine zinc insulins are demonstrated.

Comment. In this patient, with a more severe diabetes than had the preceding patients, the contrast between the effects of the various types of insulin is even more clearly discernible. The time of the onset of insulin action is clear-cut and the blood sugar concentrations rose promptly when the insulin action was exhausted. The effect of unmodified insulin was at an end by the 10th hour, that of protamine zinc insulin was exhausted at the 28th hour, and that of globin insulin at the 20th hour.

CASE 5.—H.M., a white male, aged 18, height 165 cm. (65 inches), weight 56.7 kg. (125 pounds), was admitted on January 5, 1940, with a history of having had diabetes one year. He was allowed a diet containing

protein 100 gm., fat 133 gm., and carbohydrate 300 gm. (2200 calories), and he was found to require 75 units of protamine zinc insulin with 32 units of unmodified insulin in the morning and 18 units of unmodified insulin before supper. Following the test dose of 80 units of unmodified insulin there was a prompt reduction of the blood sugar level from 264 mg. to 58 mg. per 100 cc. during the first 4 hours. After the 10th hour the blood sugar rose rapidly to high levels. A similar effect was observed following the injection of 80 units of crystalline insulin. After 80 units of protamine zinc insulin were given the blood sugar rose from a fasting level of 247 mg. to 284 mg. per 100 cc. during the first 4 hours after injection, and then gradually fell, reaching normal values between the 14th and 18th hours. The level then rose slowly although the fasting level was not regained by the 34th hour after injection of the insulin. When 80 units of globin insulin were given the blood sugar values fell, at first slowly, and then more rapidly, reaching a level of 84 mg. per 100 cc. at 10 hours after the insulin was given. The blood sugar level rose from 95 to 173 mg. per 100 cc. between the 24th and 26th hours (see Chart 5).

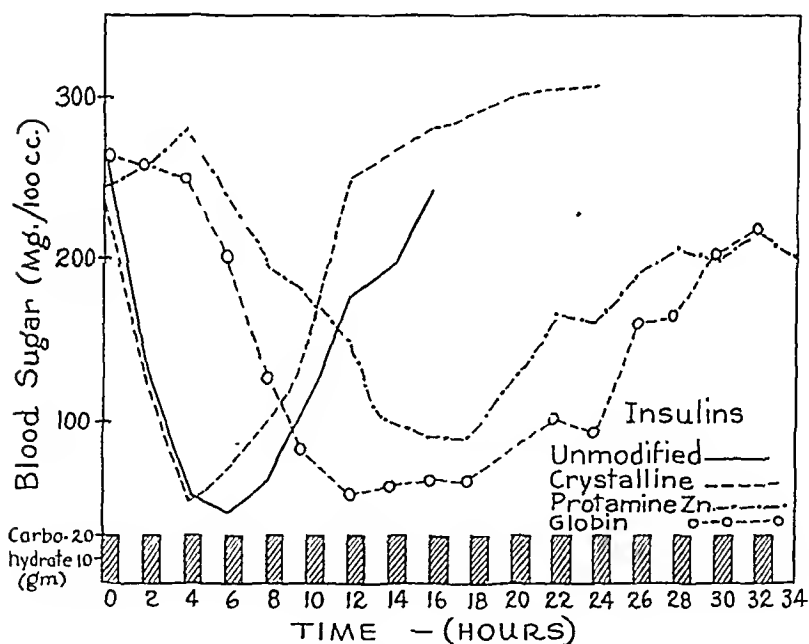


CHART 5.—Case 5 (H.M.). The intermediate effect of globin insulin (80 units) in a patient having a severe diabetes is depicted.

Comment. The results in this case depict: 1, The similarity of the speed, intensity and duration of the effects of unmodified and of crystalline insulin as has been previously observed and reported.³ 2, The definite delay in the effect of the protamine zinc insulin is typical of the results which have been described by many observers. 3, The effect of globin insulin on the blood sugar level was apparent within 2 hours and was most marked between the 4th and 12th hours, maintaining a normal or hypoglycemic blood sugar level until the 24th hour. When a larger dose (120 units) was given, in a

TABLE 1. — BLOOD SUGAR VALUES DEPICTING THE COMPARATIVE HYPOGLYCEMIC EFFECTS OF IDENTICAL QUANTITIES OF THE VARIOUS SPECIFIED INSULINS.

Case No.	Pt.	Sex.	Age.	Ht. (cm.).	Wt. (kg.).	Type of insulin.	Dosage (units).	Fast-ing.	2.	4.	6.	8.	10.	12.	14.	16.	18.	20.	22.	24.	26.	28.	30.	32.	34.
1	T.B.	M	47	172.7	70.8	Unmodified	15	92	60	76	80	89	92	101	92	105									
						Crystalline	15	84	51	49	65	77	90	96	101	89									
						Protamine zinc	15	97	89	89	88	..	77	81	78	74	76	..	76	87	114				
						Globin	15	100	89	78	86	83	81	74	80	89	90	98	104	102	107				
2	A.Z.	M	62	165.7	61.2	Unmodified	30	90	84	51	52	81	93										
						Crystalline	30	100	45	51	51	71	99	117	..	117	104	..	116	107	107	118			
						Protamine zinc	30	90	81	102	77	73	77	..	63	59	53	..	67	..	80	85			
						Globin	30	91	114	114	83	56	66	56	72	82	90	..	77	80	75	88	80	114	
3	J.J.	M	56	173.9	76.2	Crystalline	48	121	35	44	47	69	70	83	89	96	97	..	148	167	140	146			
						Protamine zinc	48	140	145	137	128	110	..	122	120	120	97	..	132	130	129	129			
						Globin	48	154	143	87	50	74	85	103	98	92	110	127	147	193	180	189			
4	D.C.	M	53	162.0	61.2	Unmodified	78	180	47	41	56	117	172	216	233	217	239	283	298	235	246	198			
						Protamine zinc	78	183	205	209	197	132	109	95	68	60	68	85	98	90	86	137			
						Globin	78	214	58	38	41	48	57	71	96	94	131	210	229	249	234	249			
5	H.M.	M	18	165.0	56.7	Unmodified	80	264	130	58	53	65	118	178	193	243									
						Crystalline	80	236	125	53	67	97	145	246	..	280	286	..	303	305					
						Protamine zinc	80	247	258	284	238	195	183	152	100	93	91	..	167	161	189	205	199	226	207
						Globin	80	264	259	253	205	127	84	55	58	63	64	..	106	95	173	176	203	223	
						Globin	120	246	270	215	145	78	56	58	46	39	48	..	60	60	64	77			

subsequent test, the blood sugar fell more rapidly and the lower level was maintained for a longer period, illustrating the importance of the size of the dose in considering the duration of action of any type of insulin.

Discussion. Globin insulin, in all but one of the subjects upon whom observations were made, had a blood sugar-lowering action which began within 2 hours after its injection. This effect reached a maximum intensity between the 2d and 8th hours, and was maintained for 18 to 24 hours. The hypoglycemic action during the first 4 hours was slower than that of identical doses of unmodified and crystalline insulin but more rapid than that of protamine zinc insulin. The period of maximum effect was observed to begin sooner and ceased somewhat earlier than when protamine zinc insulin was given. Thus from a practical application the quicker action of globin insulin tending to prevent postcibal hyperglycemia would reduce the need of supplemental doses of unmodified or crystalline insulin.

The blood sugar level reached the lowest point from the 8th to the 10th hour after the administration of globin insulin. This corresponds with the observations of Bauman that patients receiving globin insulin, in their routine treatment, are prone to have hypoglycemic reactions between 4 o'clock in the afternoon and dinner time unless appropriate shifting of the diet is made to prevent them.

In the patients who received moderately large doses of insulin (Cases 3, 4 and 5), there was a slightly greater hypoglycemic effect from the globin than from the protamine zinc insulin. Our attention was first drawn to this phenomenon during the observations upon patient H.M. (Case 5). This patient's total daily requirement had been 125 units (protamine zinc and crystalline insulin). We, therefore, decided upon 120 units as a proper test dose of each insulin. When this amount of globin insulin was given, his blood sugar level reached 56 mg. per 100 cc. on the 10th hour and normal values were not restored until the conclusion of our observations at the 28th hour. Subjectively, he was uncomfortable throughout this period and was semi-stuporous part of the time. The observations were repeated using 80 units as the test dose. Even with this amount of globin insulin the blood sugar level was as low as 55 mg. as compared with a minimum value of 91 mg. when an equal quantity of protamine zinc insulin was administered. This observation confirms our clinical experience in the routine treatment of diabetic patients; namely, that unit for unit globin insulin has a greater hypoglycemic effect than protamine zinc insulin. These studies will be the subject matter of another publication.

Summary. Observations on the comparative effects of equal quantities of unmodified, crystalline, protamine zinc and globin insulins have been made on 42 patients and the results reported in

4 diabetics and 1 normal control, all of whose carbohydrate intakes were uniform throughout the tests.

In each instance there was a distinct contrast between the effect of either unmodified or crystalline insulin which begins quickly and is soon ended, the effect of the protamine zinc insulin which is delayed in appearing and is prolonged, and the effect of globin insulin which fell between these extremes.

The blood sugar-lowering effect of globin insulin began soon after injection of the insulin and gradually increased in intensity until between the 8th and 12th hours after the injection. The effect then gradually subsided. The apparent effect of globin insulin in the non-diabetic and 2 subjects having a mild and 1 having a severe diabetes persisted for 20 hours after it was injected. In 1 patient having severe diabetes and receiving a larger dose the effect persisted for 24 hours.

Globin insulin has a quantitatively greater effect, unit for unit, than protamine zinc insulin.

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STUDIES ON THE HEMORRHAGIC AGENT 3,3'-METHYLENEBIS (4-HYDROXYCOUMARIN).

I. ITS EFFECT ON THE PROTHROMBIN AND COAGULATION TIME OF THE BLOOD OF DOGS AND HUMANS.*

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In 1921 Schofield^{18a,b} in Canada described a serious and sometimes fatal hemorrhagic disease in cattle which he attributed to the ingestion of spoiled sweet clover hay or silage. At about the same time Roderick^{16a,b,17} in this country studied the condition

* This study was aided in part by a grant from the Wisconsin Alumni Research Foundation.

extensively and concluded that the cause of the delayed coagulability was a gradual diminution in the prothrombin of the blood. Quick¹⁴ confirmed this conclusion. In 1934, Prof. K. P. Link and his associates of the Wisconsin Agricultural Experiment Station at the University of Wisconsin undertook the task of identifying the toxic factor in spoiled sweet clover. This work established the fact that the hemorrhagic agent was a dicoumarin compound. Later they succeeded in isolating and crystallizing the active principle, and have synthesized the biologically active substance and a large number of active pure crystalline derivatives. This splendid work was fully described in a series of publications^{4-7,11,12,21} in the fall of 1940 and spring of 1941. In pure state this hemorrhagic agent is optically inactive, has a low solubility in ordinary organic solvents but is soluble in dilute alkalis. It was unequivocally demonstrated by Stahmann, Huebner and Link²¹ through degradation reactions and by synthesis that the hemorrhagic agent, $C_{16}H_{12}O_6$, was the dicoumarin 3,3'-methylenebis (4-hydroxycoumarin). The chemical, physical and biologic properties of this product and of the agent occurring naturally in spoiled sweet clover were found to be identical.

In the early studies of hemorrhagic disease of cattle, Roderick observed no significant changes in the non-protein nitrogen, blood calcium, acid-base equilibrium, or icterus index. Occasionally the blood sugar was high, usually it was normal. Schofield^{18a} found upon postmortem examination gross lobular lesions in the liver to which he attributed the hemorrhagic tendency. Roderick,^{16a,b} on the other hand, observed only areas of focal necrosis, and these in but half of the cases. He believed that the lesions described by Schofield were due to postmortem change. Roderick found little evidence of serious impairment of the liver function. The hemorrhages occurred at different sites but were especially frequent in the subcutaneous tissues and in the fascia of muscles. Gross and microscopical examination of the blood-vessels did not show changes that would explain the hemorrhage.

It was recognized that if the disease with hemorrhagic manifestations was not too far advanced, it could be cured by eliminating the spoiled clover from the diet or by injecting blood serum or whole blood from healthy animals.

Experiments performed on rabbits by Quick¹⁴ indicated that the feeding of alfalfa would counteract the bleeding tendency resulting from the feeding of toxic clover, but Smith¹⁹ reported that alfalfa failed to prevent hemorrhagic sweet-clover disease. Some observations to be reported here tend to confirm the substance of these latter investigations.

We had followed with much interest the studies of Professor Link and his associates, for it was obvious that this substance might have important clinical application as a substitute for heparin in the

prevention of thrombosis. The considerable difficulty of purifying heparin, the resultant high cost, and the necessity for repeated or continuous intravenous administration made it desirable that similar agents without these handicaps be sought. The relatively low cost and the efficacy with which 3,3'-methylenebis (4-hydroxycoumarin) can be orally administered made the possibility of utilizing this material attractive.

With the synthesis of the hemorrhagic substance, large, relatively inexpensive quantities were made available for study upon larger animals and, if found feasible, upon human beings. This material was first furnished us through the kindness of Professor Link in September of 1940, since which time studies upon the pharmacologic and clinical properties have been made. The very generous cooperation of Dr. Mark Stahmann and Professor Link has facilitated this work.

It is the purpose of this communication to relate our experiences with this synthetic dicoumarin.

Prior to our study of this dicoumarin it had been established that this material produced prolongation of prothrombin time and delay in the coagulation of blood in rabbits and in dogs. It appeared to us that subsequent investigations should be directed, first, to elucidate the morphologic changes that might occur in dogs when so-called therapeutic and toxic doses were given; second, to establish the range between the effective therapeutic dose and the minimal lethal dose and thus determine the margin of safety; third, to determine whether this material reduced prothrombin in human beings as it does in cattle, rabbits and dogs; and fourth, to demonstrate, if possible, whether the administration of this dicoumarin in safe dosage would actually prolong the time of or prevent intravascular clotting. The fifth and very important point was, of course, to establish whether or not the material would prevent the development of thromboses in human beings; everything preceding is directed toward this major aim which can be settled only by extensive investigations in the future. Finally, the mode of action of the dicoumarin is important, but this matter has been little investigated to date.

Methods. Prothrombin time was determined on undiluted plasma by Pohle and Stewart's¹³ modification of Quick's technique. In both dogs and patients, one or more normal controls were always utilized for check upon the technique and potency of the thromboplastin. Thromboplastin giving a normal time of 10 to 11 seconds in human beings and 5.5 to 6.5 seconds in dogs was used. For convenience, the approximate percentages of prothrombin in human plasma were derived from the chart of Pohle and Stewart. By this estimation, a time of 12.5 seconds indicates concentration of about 50% prothrombin; 19 seconds, 25% prothrombin; and 30 seconds, 12.5% prothrombin. In dogs a prothrombin time of 7 to 8 seconds indicates an approximate reduction of prothrombin to 50% of normal; 9.5 to 11 seconds to 25% of normal; and 15 to 20 seconds to about 12.5% of normal. A time longer than 45 seconds was generally less accurate because of the

greater difficulty in determining the end point. The work of Link¹² and his associates indicates that the concentration of the plasma used will affect the absolute values (% prothrombin). The values of prothrombin in per cent are therefore presented with reserve.

The coagulation time was measured by the 2-tube method of Lee and White at room temperature. The tubes were scrupulously clean and the syringe clean and wet. Care was taken to avoid too great suction in the collection of samples, to avoid air bubbles, and to transfer the blood to the test tubes with a minimum of agitation. Times longer than 14 minutes in humans and 12 minutes in dogs were felt to be abnormal.

Materials. 3,3'-methylenebis (4-hydroxycoumarin) was used exclusively in oral administration experiments and the disodium salt of this substance was the only material used intravenously. These materials were furnished to us ready to use by Stahmann and Link.

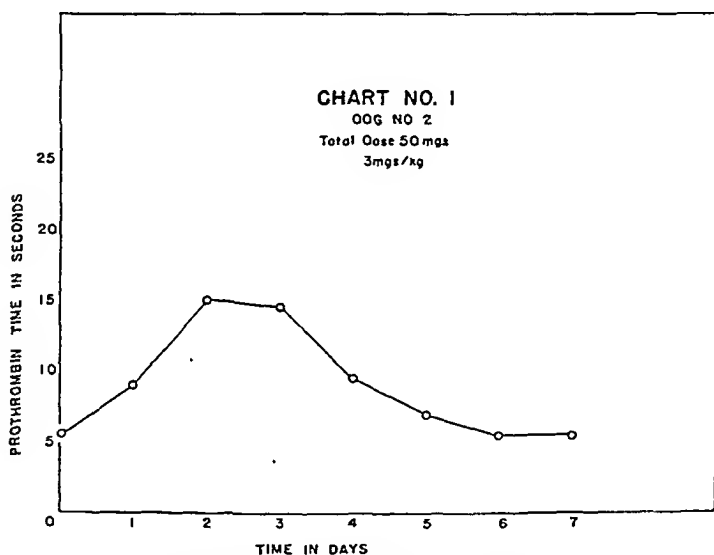


CHART 1.—The effect of a single oral dose of 3,3'-methylenebis (4-hydroxycoumarin) upon the prothrombin time of a dog.

Experiments. In all early experiments the powdered substance was given by mouth in gelatin capsules, in varying doses, to dogs that had not been fasted. In later experiments, when the approximate effective and safe dosage had been established, the disodium salt of 3,3'-methylenebis (4-hydroxycoumarin) was given intravenously to exclude the factor of variable absorption. A fairly characteristic effect upon prothrombin time of a single dose of the dicoumarin is shown in Chart 1 where 50 mg. (3 mg. per kilo) was given to Dog 2. Twenty-four hours after the material was administered the prothrombin time was slightly longer, still longer after 48 hours, attained its maximum after 48 hours, and then gradually returned to approximately the normal level on the 6th day. Chart 2 shows the effect of administration of repeated large doses to a dog

(No. 73) in which marked changes in both the prothrombin time and coagulation time were effected.

Observations in Dogs. Link and his associates demonstrated that the 3,3'-methylenebis (4-hydroxycoumarin) was capable of producing deficiency of prothrombin in the blood of animals. Heretofore, it had been demonstrated that prothrombin deficiency in man is caused by lack of absorption of the fat-soluble vitamin, as in obstructive jaundice, enteric disease, idiopathic steatorrhea, sprue, and gastro-colic fistulae.^{1,3,9,20} Deficiency of vitamin K in the newborn is presumably due to failure of bacterial synthesis.¹⁵ Prothrombin

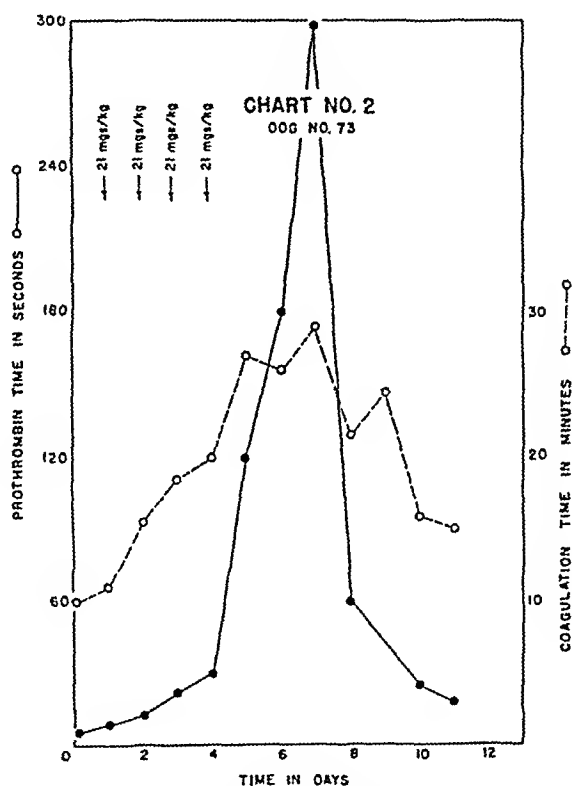


CHART 2.—The effect of repeated doses of 3,3'-methylenebis (4-hydroxycoumarin) upon the prothrombin time and coagulation time of a 14-kg. dog.

deficiency is also associated with extensive hepatic disease and here the administration of large quantities of vitamin K is often not corrective because the liver is unable to synthesize prothrombin.^{8,13} Hence, despite the report of Roderick that no gross lesion was found in the liver of cattle dying of hemorrhagic sweet clover disease, it was our feeling that one might be dealing with a potentially dangerous substance. Therefore, the early studies were directed toward evaluating the toxicity of this material in dogs.

Originally the material was given in large and repeated doses, as shown in Table 1.

TABLE 1

INCREASED ORAL DOSES OF 3,3'-METHYLENEBIS (4-HYDROXYCOUMARIN) ON PROTHROMBIN AND COAGULATION TIME IN DOGS.

INGHAM, MEYER, POHLE:

Dog No.	Weight, kg.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Remarks.
2A	10.7	6.5	10	3.8	16	300	150	17	7.5	38	300													4 hrs. Dog died 22d day; hemorrhages.
3A	12.0	6.5	23					15	20	6 hrs. 21 hrs. (+) (+)	12	7												11 30
	3.5	30	4					15	20	6 hrs. 21 hrs. (+) (+)	12	7												
5	15.4	8.5	3.5					16	5	6	18	5	27	18										
	3.2	5						360	1800	350	2 hrs. 24 hrs. (+) (+)	30	30	30	30	30	30	30	30	30	30	30	30	
6	17.7	7						23	50	26	31	31												Found dead 13th day; G. I. hemorrhage.
	5.7	29	21.5	10	10	16	5																	
7	10.2	7						28	58	2 hrs. 24 hrs. (+) (+)	12	7												Died on 11th day; bleeding gums; blood in stool.
	7.5	30	14	14	18	12		20	20	34	16	13												
11	10.7	5.5	0	14																				
	2.5	5	5	5	17	33																		
12	13.5	6.5	10	22				2.5	2.5	10	7	5												Hemorrhage from G. I. tract on 9th, 10th, 11th days; recovered.
	2.0	1.50	37																					
11	11.8	5.5																						Died on 9th day; tarry stools; subcutaneous hemorrhages.
	43	6	14.5																					
72	10.4	5.5	13	15	32	70	210	200																Killed on 12th day.
	7.5	12	18	25	11	21	29																	
73	11.2	5.5	8.5	12.5	22	30	120	180	300	60	0007	23												Died on 3d day; no hemorrhages, but widespread small vessel dilatation.
	10	11	15.5	18.5	59	27	26	29	21.5	24.5	16	17.5	0	5.5										Died on 8th day; hemorrhages from G. I. tract.
	21	21	21	21								16	12	10										Bleeding on 5th day; dead on 7th day.
																								Recovered.

* First Row: Prothrombin time in seconds.

† Second Row (italics): Coagulation time in minutes.

‡ Third Row: Dose mg. per kilo.

* First Row: Prothrombin time in seconds.

↑ Second Row (*italics*): Coagulation time in minutes.

† Third Row: Dose mg. per kilo.

Dog 6, after the development of hemorrhage, recovered and Dog 11 died after showing marked prolongation in coagulation.

The death of these animals could usually be predicted 2 or 3 days in advance. They became listless, had dyspnea, tachycardia and fever, and gave evidence of hemorrhage internally, externally or both. Tarry stools were often observed. The symptoms of a single massive fatal dose given orally or intravenously were different and will be discussed below.

Postmortem examination was made of 25 dogs, including gross and microscopic examination. Hemorrhage at some site was demonstrable in all dogs. In all cases there was subcutaneous and intramuscular hemorrhage. Frequently there was gross hemorrhage in the gastro-intestinal tract and in the pleural spaces, and multiple small hemorrhages of the lungs. In no instance was there demonstrated, grossly or microscopically, significant parenchymatous disease of the liver, kidney, or other organs. Occasionally, there was evidence of moderate hydropic degeneration of the liver but nothing more. There was, however, in most of the animals that received fatal doses, marked dilatation of capillaries, small arteries and veins. This was especially marked in those animals that died acutely from massive doses. No lesions in the walls of the vessels were demonstrable. This vascular dilatation was widespread in all viscera and was very striking. It impressed us greatly, since it was also observed, sometimes in lesser degree, in animals receiving non-fatal doses that were sacrificed for pathologic study.

The average oral dose per kilogram administered to the 6 dogs that died varied from 71 to 282 mg. per kilo. It has been repeatedly demonstrated that the fatal oral dose varies considerably and that a single massive dose is less likely to kill than are divided doses. This is exemplified in Dog 15 of Table 2, which received 5000 mg. (415 mg. per kilo) and yet survived with only moderate prolongation of the prothrombin time. Dog 72 of Table 1, on the other hand, died after a total dosage of only 1200 mg. (116 mg. per kilo), given in four divided doses. However, small doses of 3,3'-methylenebis (4-hydroxycoumarin) can be given for long periods without apparent toxicity. Thus 2 dogs of 14 and 15 kilos each received 10 mg. of the material daily for 26 days without symptoms or prolongation of the prothrombin time, indicating that there is not a large factor of cumulation in subminimal effective doses.

In Table 2 is shown the effect of oral administration of single doses of 3,3'-methylenebis (4-hydroxycoumarin) upon the prothrombin time of dogs. The doses were quite variable, and the maximal dose of 5000 mg. to Dog 1 produced death in 15 hours, the dog demonstrating marked dyspnea, convulsions, coma, and hyperthermia before death but no hemorrhagic manifestations during life or at autopsy. It will be noted that there is, within limits, some correlation of prothrombin time prolongation with the size of the dose of

the dicoumarin, as will be shown later. However, there may be marked exceptions to this rule. Doses as small as 2 mg. per kilo produced significant prolongation of the prothrombin time and a dose of 90 mg. per kilo by mouth in Dog 2 produced gross prolongation of prothrombin time, to 300 seconds. In smaller single doses by mouth, 3 to 8 mg. per kilo in dogs, significant changes in the prothrombin time were routine, but significant changes in the coagulation time could be demonstrated only occasionally.

TABLE 2.—EFFECT OF SINGLE ORAL DOSES OF 3,3'-METHYLENEBIS (4-HYDROXY-COUMARIN) UPON PROTHROMBIN TIME IN DOGS.
(Prothrombin time in seconds.)

Dog No.	Oral dose per dog, mg.	Dose per kg., mg.	Days: 0	1	2	3	4	5	6	7	8	9	10	11
1	5000	300	5 5*											
2	50	3	5 5	9	15	14 5	9.5	7	5 5	5 5				
2†	1500	90	5 5	10	38	16‡	300	150	17	7 5				
3	100	7 8	6	8	16 5	11	20	16	15 5	9	7	8	6	
4	200	11 5	6	15	24		15‡							
4†	230	13	6 5		16	24 5‡								
15	5000	415	6	10	15 5		20							8
41	50	7	6	8	18 5		9 5		6					
44	50	5	6	7 5	12		5 5							
45	50	1 4	5 5		11	9	6 5							
46	50	2	6		9 5	9	7							
47	50	3 3	5 5		10	13	7 5							
48	50	2 5	5 5		8	8	5 5				6			
52	50	3 5	5 5		10	8	7							
53	50	12 5	6		10		7							
54	50	3 3	6		11 5	9 5	7							

* Dead in 15 hours (no hemorrhage).

† Interval of 2 months between first and second experiment.

‡ Killed for pathologic study.

In no dog other than No. 1 of this group were symptoms of any type demonstrable, as a result of administration of the dicoumarin.

During the course of the experiment 6 dogs (Nos. 41, 44, 45, 46, 47 and 48) received 2 mg. of Proklot-Lilly (2 methyl-1, 4-naphthoquinone) by mouth daily, the first dose being given the day the dicoumarin was administered. Dogs 52, 53 and 54 received 1 mg. of Synkamin-Parke-Davis (4 amino-2 methyl-1 naphthol) intramuscularly daily. Neither the oral nor the intramuscular administration of the vitamin K appeared to have any effect whatever upon shortening the prothrombin time which had been prolonged by the dicoumarin.

Intravenous Administration of the Dicoumarin. The administration of the disodium salt of 3,3'-methylenebis (4-hydroxydicoumarin) intravenously has been carried out in 21 dogs. Single doses varying from 0.5 to 50 mg. per kilo were given. Doses of 35, 40 and 50 mg. per kilo were each given to 2 dogs, and all 6 dogs died within 18 hours after administration. Before death, the dogs became

dyspneic and comatose. Fever as high as 110° has been recorded. None demonstrated hemorrhage before death or at autopsy. One animal that received 20 mg. per kilo died on the 7th day after the dicoumarin was given, from hemorrhages in the small and large bowel, but one animal survived a dose of 31 mg. per kilo with only transient symptoms and without evident hemorrhage.

TABLE 3.—EFFECT OF INTRAVENOUS DOSES OF 25 MG. PER KILO OF 3,3'-METHYLENEBIS (4-HYDROXYCOUMARIN) UPON THE PROTHROMBIN TIME AND COAGULATION TIME OF DOGS.

Dog No.	Wt., kilo.	Total dose, mg.	Days: 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
74	14 2	355	5.5* 11 5†	9 47	13 9	22 17	33 21	35 17	12 5 19	8 11	6 5 6.5	7 16 5	7 5 12.5	5 5 7 5			
75	10.2	255	5 5 9 5	12 9	13 11	130 17	145 29	900 22	240 21	60 20	45 15 5	45 57	8 8	6 9 5	6 9 5	6 5 9	5 5 6 5
76	13 2	330	5 5 6 5	9 11	16.5 11 5	24 14	39 21	26 16	120 16	40 16	150? 12	12 5 11 5	30? 7 5	10 6	10 9 5	7 5 6 5	5 5 5.5

* FIRST ROW: Prothrombin time in seconds.

† SECOND ROW (*italics*): Coagulation time in minutes.

Doses of 1 to 2 mg. per kilo characteristically increased the prothrombin time from 5 or 5.5 seconds to a maximal of from 9 to 11.5 seconds on the second day after administration, and invariably the prothrombin time was normal on the 4th day. Larger doses produced a more profound and sustained effect. The effect upon the prothrombin time and coagulation time of administering 25 mg. per kilo to 3 dogs of a single experimental group is shown in Table 3. In none of these dogs were there symptoms other than slight dyspnea for a few hours. It appears from these and other experiments that 25 mg. per kilo is close to the maximal intravenous dose for dogs.

Intravascular Clot Formation. It has been demonstrated that the decrease in prothrombin in humans as a result of vitamin K deficiency was only occasionally associated with a prolongation of coagulation time until the level of prothrombin was dangerously low, 30% of normal or less. Hence it was our feeling that it might be unsafe to administer this hemorrhagic agent to man in dosages that would produce reduction of prothrombin concentration to less than 40% to 50%, nor to reduce it sufficiently to cause prolongation of the coagulation time. It was believed, however, that if the prothrombin was reduced to about 50% of normal, and maintained at this level, intravascular clotting might be retarded even though clot formation in a test tube was not prolonged. Hence studies were made in an attempt to demonstrate that intravascular clotting could be prolonged by the administration of 3,3'-methylenebis (4-hydroxycoumarin) in doses which appeared to us to be safe for

Observations on Humans. From the first, despite the apparent high tolerance and high therapeutic index of 3,3'-methylenebis (4-hydroxycoumarin) for dogs, we approached the problem of its administration to humans with temerity. The first 12 patients to receive the material were, with but 1 exception, patients with advanced malignancy. Only 1 demonstrated definite clinical evidence of involvement of the liver.

TABLE 4.—EFFECT OF 3,3'-METHYLENEBIS (4-HYDROXYCOUMARIN) ADMINISTERED INTRAVENOUSLY TO PATIENTS.

Pt.	Sex.	Diagnosis.	Wt., kg.	Dose, mg./kg.	Days: 0	1	2	3	4	5	6	7	8	9
S. C.	M	Peptic ulcer	74	1 7	12* 11	15 5 15	15 5 18	13 5 11	15 5 15	12 12 5	11 5 12	12 15 5	12 14 5	12 7 5
G. G.	F	Bronchiogenic carcinoma	60	2 0	12 5 5	16 12	16.5 14	14.5 8 5	Discharge	d				
O. N.	M	Arteriosclerosis; asthma	70	3 0	12 9 5	15 16	16 21	15 23	18 23	16 13 5	12 12	12 12	12 16	12 12.5
A. W.	M	Arteriosclerosis	73	4 0	12 10 5	18 8 5	22 5 18	22 16	13 8 5	12 15	12 11			
A. L.	M	Psychoneurosis	66	4 0	12 7	14 13	17 7 5 ?	15 14	11 5 7 5 ?	12 15.5				
D. B.	M	Silicosis	80	4 0	11 5 8 5	15 14	22 5 18 5	24 16	14 14	12 15	12 13 5			

* Control time for this particular supply of thromboplastin was 12 seconds. Dilutions of normal plasma to 50% gave a time of 16.5 seconds; dilution to 40% gave a figure of 23 seconds with this thromboplastin.

† First Row: Prothrombin time in seconds.

‡ Second Row (*italics*): Coagulation time in minutes.

In all observations on humans complete blood counts, urinalyses, and blood sugar determinations were made. For several the hipuric acid liver function test, the icterus index, and the cephalin-cholesterol test of Hanger,¹⁰ complete blood counts and platelet counts, bleeding and coagulation times were done before the dicoumarin was administered. In no instance were gross changes in these findings observed after administration of the dicoumarin. All these patients received the material in gelatin capsules, orally. The first patient received 10 mg. of the dicoumarin on the 1st, 3d and 5th days, 25 on the 6th, and 50 mg. on the 10th day of observation. The other 11 patients, with 1 exception, received single doses ranging from 50 to 100 mg. (0.75 to 2 mg. per kilo). In 5 of the 11 patients the prothrombin time was prolonged from an average control level of 10 seconds to an average maximal level of 12 between the 2d and 6th day after the material was administered. These changes, while not marked, appear to us to be significant, since the doses were small. Six patients to whom similar dosages were admin-

istered showed no prolongation in the prothrombin time. In none of the 12 patients was there the slightest clinical evidence to indicate that the dicoumarin was unfavorably borne. Butt, Allen and Bollman² have given human beings much larger doses than we have administered without the development of toxic symptoms.

The disodium salt of 3,3'-methylenebis (4-hydroxycoumarin) was given intravenously to human beings because of the apparent variation in absorption when it was given orally. It was thought that the effective therapeutic dose might thus be more readily established. To date this material has been given to 10 human beings in doses ranging from 0.5 to 4 mg. per kilo without the development of any toxic symptoms. The effects of the larger doses upon the prothrombin time and coagulation time for 6 of these are shown in Table 4. The first 4 cases are omitted because the doses were smaller, 1 mg. per kilo or less, and produced no discernible effects. The maximal therapeutic dose and the optimal effective dose is not as yet established.

Complete blood counts with platelet estimations, repeated urine analyses, blood sugar and non-protein nitrogen determinations, and icterus indices were done on all patients at the beginning and end of the experimental period. Hippuric acid and cephalin cholesterol determinations were made on 4 of the patients before and after the experimental period. No significant changes were noted.

The results show a distinct effect upon both the prothrombin time and the coagulation time. The control levels of prothrombin in this particular group of experiments are higher than usual for human beings with the technique we use, but can be explained by the fact that the thromboplastin of this particular time was somewhat less potent than that which we usually made. This variation in thromboplastin occasionally occurs, even when it is fresh, and thus the need for control observations.

It would seem from these results that rather small doses, 100 to 300 mg. (2 to 4 mg. per kilo) are sufficient to prolong the coagulation time very significantly. Some might even consider these levels hazardous, for the possibility of internal or intracranial hemorrhage must be considered. On the other hand, the results strongly suggest the possible efficacy of the material in preventing thromboses.

The variation in the effects resulting from doses of different sizes is striking. For example, 3 mg. per kilo in Patient O. N. produced a more profound effect upon the coagulation time, but not upon the prothrombin time, than did doses of 4 mg. per kilo given to Patients A. W., A. L. and D. B. This observation calls for considerable thought and emphasizes that the proper and safe dosage is yet to be worked out. It also emphasizes the need for considerable caution in prescribing the dicoumarin until further data are available.

In Vitro Experiments. The possibility that the 3,3'-methylenebis (4-hydroxycoumarin) might prolong the prothrombin time *in vitro*

was considered. To exclude this possibility, in both dogs and human beings, oxalated plasma of 2 dogs and 12 humans was obtained. To 0.1 cc. of the plasma of each was added 0.1 cc. of water and to a second, third and fourth set of test tubes containing 0.1 cc. of the plasma of each, was added 0.1 cc. solution of dicoumarin of three different levels of pH, 7.3, 7.8 and 8.5. The solutions were then incubated for periods of from 2 minutes to 3 hours. Although the prothrombin time increased with the longer incubation periods, from 10 to 25 seconds in some instances, the prolongation in the controls, where only water had been added, was as great in every experiment. It must, therefore, be concluded that this dicoumarin does not prolong the prothrombin time in dog or human plasma *in vitro*. This confirms the observations of Link and his coworkers.^{4,7,12}

Discussion. It is evident that 3,3'-methylenebis (4-hydroxycoumarin) synthesized by Stahmann, Huebner and Link is fully capable of producing prolongation in the prothrombin time and coagulation time in dogs and humans. The material is effective when administered orally or, as the disodium salt, intravenously. The prolongation in prothrombin time is not effective until 24 hours after administration of the material by mouth, and there is a similar but perhaps slightly shorter latent period with intravenous administration. For some days, varying with the dose, the prothrombin time becomes increasingly prolonged, and then, if no more than the single dose is given, gradually returns to normal, usually between the 5th and 7th day when small doses are given, by the 7th to 10th when large doses are given. Whatever the size of the dose, the initial latent period was always observed and during the first 2 days the prolongation of prothrombin times were approximately the same. Only after this period did the larger doses exhibit the greater depression of prothrombin activity. Divided doses given orally were more effective in reducing the prothrombin than was the same quantity given in a single dose; this suggested that above a certain level there is some difficulty with absorption of the material. Link¹² and his coworkers have reported recovery of considerable quantities of the dicoumarin in the feces of animals given massive doses by mouth.

The ideal dosage of the dicoumarin for human beings is not yet established, but it may be said, on the basis of studies in dogs, that the maximal tolerated dose when given intravenously is almost certainly not much greater than 25 mg. per kilo and perhaps less. From our experiments it was suggested that doses of 2 to 4 mg. of the disodium salt given intravenously are probably safe; such doses prolong the prothrombin time to about 40% to 50% of normal and usually prolong the coagulation time significantly. Similar dosage by mouth is probably also adequate. The timing of repeated doses is yet to be worked out by many observations; for the present they should be individualized by daily determinations of the prothrombin time and coagulation time. Butt, Allen and Bollman²

have given single doses of 1000 mg. orally, apparently without resultant toxicity.

It is suggested, but not established by experiments in dogs, that intravascular clotting may be prolonged by the previous administration of the dicoumarin in moderate dosage. Further study of this problem is contemplated but it is technically a difficult one, and an ideal method of studying intravascular clotting is difficult to attain.

The treatment of toxic symptoms or signs is confined at present to the control of prothrombin and coagulation times. From the experiences of Schofield, Roderick, Butt, Allen, and Bollman and ourselves, transfusions of serum or whole blood will cause a prompt lowering of prothrombin and coagulation times. This effect is not sustained and may have to be repeated if the coagulation time returns to dangerous levels.

The frequent observation of profound capillary dilatation that follows administration of dicoumarin, as demonstrated at autopsy, even when only moderate doses are given, raises the question of a gross vascular factor in the hemorrhagic manifestations of sweet clover disease in cattle. This factor as a possible contributing mechanism in the production of undesirable bleeding when the dicoumarin is used clinically must be borne in mind.

The mechanism by which the dicoumarin prolongs the prothrombin time, and hence the coagulation time, is not known. Even when fatal doses were given to dogs, there were no demonstrable gross or microscopic changes in the liver which could be attributed to the substance administered. It might be hypothesized that the formation of prothrombin in the liver is physiologically inhibited, and that only when the prothrombin present in the blood at the time of administration of the dicoumarin is used up, is there demonstrable prolongation in the time. This would furnish an explanation for the usual latent period of 24 hours or more before the prothrombin time is increased. The possibility that the function of prothrombin formation by the liver is inhibited is strengthened by the fact that vitamin K administration in adequate dosage is ineffective in preventing the increase in prothrombin time. Other possibilities to explain the effect of 3,3'-methylenebis (4-hydroxycoumarin), of course, come to mind, although experimental evidence for them also is lacking. Thus the material may, during the latent period, undergo change* of some type in the body before it is capable of functioning; or the prothrombin produced in the presence of the hemorrhagic agent is altered in such a way that it is inactive; or immediately after administration a protective mechanism may be set up *in vivo* which prevents the toxic substance from affecting the prothrombin. The

* Studies underway by W. R. Sullivan, R. S. Overman, M. A. Stahmann and K. P. Link indicate that the lag period is most likely due to the fact that the effect of the dicoumarin does not become apparent until it has undergone change in the animal organism.

possibility that the hemorrhagic agent inactivates the vitamin K in the body, and even the vitamin K administered subsequent to administration of the dicoumarin cannot be excluded as a cause for the decrease in prothrombin. This material is ineffective in prolonging the prothrombin time in plasma *in vitro*.

The possible importance of 3,3'-methylenebis (4-hydroxycoumarin) as a substitute for heparin in the prevention of thrombosis is self-evident. The material can be readily prepared at a reasonable cost. It can be given orally or intravenously with prolonged effect. It is possible that it may, in the future, replace heparin. But much is yet to be done. Our knowledge is still of an experimental nature and we feel that its indiscriminate use may be very hazardous, even though the therapeutic index appears to be high. It is urged that those who employ this material continue to select the patients carefully, avoiding those with gross hepatic disease, and that for the present the apparent minimal effective doses be used. It is our plan to continue the study of this interesting substance in the hope of establishing its safety and its value in the prevention and treatment of thrombosis. Its possible advantages in the prevention of adhesions, and in vascular surgery and other situations where heparin has been used remain to be investigated.

Conclusions. The synthetic dicoumarin 3,3'-methylenebis (4-hydroxycoumarin) when administered orally or intravenously produced, after a usual latent period of 24 hours or more, prolongation of prothrombin time and coagulation time in dogs and human beings.

Therapeutic and fatal doses of this material given to dogs did not produce significant pathologic changes in the liver or other parenchymatous organs but did, in many instances, produce capillary, arteriolar and venule dilatations.

No harmful effects were observed from the administration of the dicoumarin to humans.

The administration of synthetic vitamin K did not shorten the prothrombin time previously lengthened by administration of the dicoumarin, but transfusion of blood was temporarily effective in shortening the prothrombin time and coagulation time after they had been prolonged.

This dicoumarin may well prove to have an important place in clinical medicine as a substitute for heparin in the prevention and treatment of thrombosis and in other conditions.

Dr. John C. McCarter examined the pathologic sections for us and Miss Emily Gray prepared the tissues. We wish gratefully to acknowledge their valuable aid.

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A GLOBULIN-FRACTION IN RABBIT'S PLASMA POSSESSING A STRONG CLOTTING PROPERTY.

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IN the course of work on the purification of rabbit plasmas it was observed that a certain fraction obtained from these plasmas was capable of producing clotting when added to plasma or blood. A description of some investigations into the nature of this substance with a summary of our findings is given in this paper.*

Method. A study was made of several fractions of rabbit plasma prepared by successive precipitating with ammonium sulphate.† The first fraction was that precipitated by the addition of 200 gm. of ammonium sulphate crystals to each liter of diluted rabbit plasma. The precipitate was twice redissolved in distilled water in one-half of the original volume and reprecipitated at about 20% ammonium sulphate. The final precipitate was dialyzed for 2 days in tap water; this fraction was designated *I-W*. In some cases an acid-insoluble portion was removed from the practically salt-free dialysate. Acidification of the dialysate to pH 5.3 with normal lactic acid and dilution with distilled water if indicated by preliminary test, generally removed all water-insoluble proteins. Occasionally a second, but relatively small, fraction of water-insoluble protein could be eliminated by subsequent adjustment to pH 5.8. These water-insoluble proteins were suspended in 1% salt solution at neutrality; they were designated *I-WI*. The water-soluble proteins were adjusted to neutrality, 1% sodium chloride was added, and the material was concentrated by ultrafiltration. This fraction was identified as *I-WS*.

The second fraction was precipitated by the addition, to each liter of filtrate after removal of the first fraction, of 100 gm. of crystalline ammo-

* A preliminary report on this subject was published in *Science*, 93, 328, 1941.

† We are indebted to Mr. James Jacques for technical assistance in this fractionation.

nium sulphate. As in the case of the first fraction, the precipitate thus obtained was twice redissolved in distilled water and reprecipitated at 30% ammonium sulphate. After that the precipitate was dialyzed for 2 days in tap water; it was identified as *II-W*. Further separation into water-insoluble (*II-WI*), and water-soluble (*II-WS*), fractions was effected in a manner similar to that employed with the first fraction.

Addition of 200 gm. of crystalline ammonium sulphate to each liter of filtrate after removal of the second fraction precipitated the third fraction. This made a total of 500 gm. of ammonium sulphate per liter of original plasma. All the thermolabile proteins of rabbit plasma are precipitated at this concentration of ammonium sulphate. This third precipitate was dialyzed for 2 days in tap water; it was identified as *III-W*. Acidification of the dialysate of this fraction to pH 5.3 yields a very small water-insoluble fraction (*III-WI*). The greater part of the proteins of the third fraction is water-soluble (*III-WS*). This third fraction contains the greatest portion of the proteins of rabbit plasma.

Many batches of rabbit plasma were fractionated in this manner, and the fractions were studied for their clotting power.

Experiment With Plasma. To 0.9 cc. of the plasma in a Wassermann tube was added 0.1 cc. of the material under test. The tube was then placed in the water-bath at 37° C., and the clotting time was recorded.

Preliminary experiments have consistently demonstrated that the precipitate obtained from rabbit plasma at between 20% and 30% (200 and 300 gm. per liter) of ammonium sulphate possesses practically all of the clotting power of the original plasma. This fraction (*II-W*) will be referred to as clotting globulin. More detailed study showed that a considerable portion of the clotting factor could be precipitated with the water-insoluble proteins *II-WI* at pH 5.3 in the absence of salt.

TABLE 1.—THE CLOTING OF HORSE PLASMA CONTAINING 1% SODIUM CITRATE BY DIFFERENT FRACTIONS OF RABBIT PLASMA.

Dilutions of test material with normal horse citrate plasma	Fraction <i>I-W</i> .		Fraction <i>II-W</i> .		Fraction <i>III-W</i> .	
	Water soluble at pH 5.2	Insoluble at pH 5.2	Water soluble at pH 5.2	Insoluble at pH 5.2	Water soluble at pH 5.2	Insoluble at pH 5.2
	<i>I-WS.</i>	<i>I-WI.</i>	<i>II-WS.</i>	<i>II-WI.</i>	<i>III-WS.</i>	<i>III-WI.</i>
	NR9-1.	NR9-4.	NR9-2.	NR9-5.	NR9-3.	NR9-6.
	Solids 12.1%.	Solids 13%.	Solids 12%.	Solids 7.3%.	Solids 12.7%.	Solids 1.7%.
	Figures indicate time, in minutes, within which clotting occurred.					
1:10	—	—	30	Less than 1	—	—
1:100	—	—	30	Less than 1	—	—
1:200	—	—	60	Less than 1	—	—
1:500	—	—	60	Less than 1	—	—
1:1000	—	—	—	8	—	—
1:2000	—	—	—	60	—	—
1:5000	—	—	—	60	—	—
1:10000	—	—	—	—	—	—

All fractions were prepared from normal rabbit plasma.

Failure to clot within 24 hours is indicated by a dash (—).

Horse, rabbit and human plasmas were secured by drawing blood from the vein into vessels containing potassium oxalate solution, in the proportion of 9 cc. of whole blood to 1 cc. of 2.6% potassium oxalate solution. The plasma was then freed of red cells by centrifugation. In a Wassermann tube, 0.9 cc. of a given plasma was mixed with 0.1 cc. of rabbit fraction number 356-6, in varying dilution; the mixtures were then placed in the water-bath at 37° C. and the clotting times were noted. This material (No. 356-6) represents the second fraction of rabbit plasma; more specifically, that part of rabbit plasma which is insoluble in water at pH 5.2 (*II-WI*). The content of solids of this material was 16.6%. All three plasmas, from the horse, the rabbit and man were clotted by the material under test.

TABLE 2.—THE CLOTING OF THE PLASMA FROM DIFFERENT SPECIES OF ANIMALS BY THE SECOND FRACTION ISOLATED FROM RABBIT PLASMA (SPECIMEN No. 356-6).

Dilution of test material, with plasmas	Normal horse plasma.	Normal human plasma.	Normal rabbit plasma.
	Time in which clotting occurred.		
1:10	5 sec.	5 sec.	5 sec.
1:100	20 sec.	10 sec.	5 sec.
1:1000	210 sec.	15 sec.	10 sec.
1:5000	24 hrs.	6 min.	4 min.
1:10000	—	60 min.	60 min.
Control*	—	—	—

* One volume of 0.85% NaCl mixed with 9 volumes of plasma. Failure to clot within 24 hours is indicated by a dash (—).

A study was made on the clotting, by rabbit's plasma fraction *II-W'*, of normal horse plasmas prepared with different anticoagulants. The anticoagulants employed were: 1, Potassium oxalate, the final concentrations in the plasmas being 0.1%, 0.5%, 1%. 2, A commercial preparation of heparin; 1 mg. of which, according to the specifications, prevents the coagulation of 5 cc. of cat blood for 24 hours. In our experiments the final concentration of heparin in the plasma was 0.05% or 0.1%; with such concentrations, horse plasma would remain fluid for more than 24 hours. 3, Germanin; final concentrations in the plasma of 0.15%, 0.2%, 0.4%.

The clotting substance used was rabbit plasma fraction *II-WI*, with a content of solids at 7.3%. The technique followed has already been described. The findings of this series of tests are shown in Table 3.

It was observed that the action of clotting globulin (*II-W'*) is largely independent of the nature and concentration of the anticoagulant within the range of the substance tried. Increasing the final concentration in the plasma of potassium oxalate to as much as 1% serves only to delay, but does not stop, the clotting of normal horse plasma by fraction *II-W'* of rabbit plasma. It should also be mentioned here that the clotting of normal horse plasma

containing 1% sodium citrate by rabbit plasma fraction *II-W* has been regularly observed.

TABLE 3.—THE INFLUENCE OF THE ANTICOAGULANT ON THE CLOTTING OF NORMAL HORSE PLASMA BY RABBIT PLASMA FRACTION *II-W*.

Dilutions of Fraction <i>II-WI</i> with normal horse plasma.	POTASSIUM OXALATE.		HEPARIN.		GERMANIN.		
	Final concentration of anticoagulant in the plasma.						
	0.1%.	0.5%.	1.0%.	0.05%.	0.10%.	0.1%.	0.2%.
	Time in which clotting occurred.						
1:10	1 min.	10 min.	20 min.	1 min.	1 min.	1 min.	2 min.
1:100	1 min.	10 min.	20 min.	3 min.	3 min.	1 min.	—
1:1000	2 hrs.	24 hrs.	24 hrs.	—	—	2 hrs.	—
1:2000	—	—	—	—	—	—	—
1:5000	—	—	—	—	—	—	—
1:10000	—	—	—	—	—	—	—

The particular Fraction *II-W* used was No. NR9-5.

Failure to clot within 24 hours is indicated by a dash (—).

Clotting globulin was observed to clot rapidly horse plasma deprived of its own prothrombin by absorption with magnesium hydroxide. Horse plasma containing 0.26% potassium oxalate was mixed with 10% of its volume of a 3% suspension of magnesium hydroxide. The mixture was shaken several times in the next 2 hours at room temperature, after which it was centrifuged and the reaction of the supernatant absorbed plasma was adjusted to neutrality. Such absorbed plasma does not clot on recalcification; however, the addition of the above described clotting globulin (*II-W*) in small quantities was able to clot it.

Experiments With Whole Blood. In this work the 15 by 150 mm. test tube, coated inside with a thin even layer of paraffin, was used. When 1 cc. of physiologic salt solution and 9 cc. of whole blood are mixed in such a tube, the average clotting time at room temperature is between 25 and 30 minutes. The introduction into such a preparation of very minute portions of rabbit fraction *II-W* considerably reduces the clotting time. Tests of this kind, using fractions No. NR9-5 and No. 356-6 on whole horse blood, are reported in Table 4.

TABLE 4.—THE CLOTTING OF WHOLE HORSE BLOOD BY FRACTION *II-W* (SPECIMENS NR9-5 AND 356-6).

Dilutions of test material with whole horse blood.	Specimen NR9-5.			Specimen 356-6.
	Exp. 1.	Exp. 2.	Exp. 3.	Exp. 4.
	Time in which clotting occurred.			
1:10	10 sec.	15 sec.	10 sec.	
1:100	40 sec.	45 sec.	5 sec.	
1:1000	1 min.	1 min.,	20 sec.	1 min.,
		20 sec.		30 sec.
1:10000	3 min.	6 min.,	5 min.,	4 min.
		40 sec.	15 sec.	
1:100000	10 min.,	10 min.,	2 min.,	18 min.
	25 sec.	35 sec.	5 sec.	
Control	30 min.,	16 min.,	25 min.	44 min
(1 vol. physiologic saline, 9 vols. whole blood)	25 sec	30 sec.		

The Relative Toxicity of the Three Rabbit-plasma Fractions. In the fractionation of immune rabbit plasma with ammonium sulphate, as referred to in an earlier part of this paper, the major portion of the antibodies has been found in fraction *I-W*.

Tests of Toxicity in Mice. It was shown that there is a marked difference in the toxicity of the three fractions so obtained. For example, mice were not obviously affected by the intravenous injection of 0.4 cc. of fraction *I-WI*, or of fraction *III-WI*, containing 12% solids. Fraction *II-WI*, however, proved to be lethal for mice, when injected intravenously. Each of 2 mice received an intravenous injection of 0.01 cc. of fraction *II-WI*, No. NR9-4 (12% solids) prepared from normal rabbit plasma; in a few minutes both mice were dead. Similarly, when each of a series of 6 mice received intravenously 0.01 cc. of No. 13C14-4 (10% solids) a preparation of fraction *II-WI* from rabbit antimeningococcal plasma, each animal died within a few minutes.

Fraction *II-W*, when injected subcutaneously or into the abdominal cavity of the mouse is more easily tolerated. Two mice, each receiving 1 cc. subcutaneously of No. 13C14-4 survived for 2 weeks.

Tests in Rabbits. The "toxicity" of the clotting globulin was also studied in the rabbit for the purpose of determining whether the lethal effect is due to intravascular clotting. This was found to be the case.

Rabbit 1 (5 pounds) received 1 cc. clotting globulin 13-C-19 intravenously (slowly). Death occurred in 2 minutes. Autopsy immediately. Right auricle and ventricle filled with completely clotted blood, the clot extending into the pulmonary artery filling it. The left chambers of the heart contained little fluid blood.

Rabbit 2 (5 pounds) received 0.25 cc. clotting globulin 13-C-19 intravenously; not slowly. No symptoms. After 7 minutes 0.5 cc. clotting globulin 13-C-19 intravenously (opposite ear, slowly). No symptoms at any time.

Rabbit 3 (8½ pounds) received 1 cc. clotting globulin 13-C-19 intravenously, slowly. No symptoms in 5 minutes. Then injected another quantity of 1 cc. clotting globulin 13-C-19 into the other ear; death occurred in 2 minutes. Autopsy showed right ventricle filled with mostly fluid blood; a thin clot was found extending into the pulmonary artery in which it was deeply attached.

The Stability of the Clotting Factor Associated With Fraction II-W. In a review of a large number of batches of rabbit plasma processed up to the present, in no instance have we failed to obtain an active clotting globulin. Using the technique of testing described earlier in this paper, one volume of such a preparation may be found to clot 100 volumes of oxalated horse plasma within 30 seconds, and to clot 1000 volumes of plasma within ½ hour. The usual preparations of fraction *II-W* have a solids content of about 10%.

Our experiments have indicated that this clotting globulin is

comparatively stable. For instance, specimen No. NR6-2 (fraction II-W) was kept for 6 months at about 5° C., without preservative, with no appreciable alteration of clotting titer. Several other preparations of fraction II-W, containing 0.4% phenol and 1 to 50,000 phenyl mercuric acetate, were passed through a Berkefeld filter candle. After 9 months' storage at 5° C. the material still had considerable clotting power, though the titer was somewhat reduced.

A series of experiments has shown that heating somewhat weakens the clotting factor, but does not entirely destroy it. Even after being heated at 75° C. for 10 minutes, some of this material was able to clot 10 times its volume of plasma. Preservatives enhance the deterioration caused by heat; in this respect phenol is more destructive than merthiolate, in the concentrations tested.

The clotting fraction may be frozen and thawed without alteration of its clotting power.

The proteins associated with the clotting factor may be precipitated with 70% and 90% acetone. The redissolved precipitate possesses the clotting titer of the original material.

Discussion. Leo Loeb^{8a-c,9,10,11a,b,12,16} has reported that the intravenous injection of heterogenous serum may bring about the clotting of blood in the vessels. He has observed intravascular clotting in the pulmonary blood-vessels of rabbits injected with dog serum. Loewit⁷ attached considerable importance to this observation, feeling that it would assist in the evaluation of the primary toxicity of serum.

Loeb's findings have been of value to us as a guide in the purification of rabbit sera. In our efforts to free immune rabbit sera of its clotting action, we isolated a small globulin fraction having a clotting power of a very high order. In the studies of the activity of this preparation we have been using the technique outlined by Quick, Smith, *et al.*^{15a,b,19a,b,20-26}

The rôle of calcium in the mechanism of the clotting of blood was discussed not long ago by Howell⁶ and Mellanby.¹⁴ The clotting globulin that we have isolated from rabbit's blood, does not need calcium and has shown much strength in the presence of excess of oxalate, citrate and other anticoagulants. This clotting globulin acts directly on fibrinogen and is able to clot plasma whose own prothrombin has been absorbed with magnesium-hydroxide. Preparations of this material have been proven to be comparatively stable.

From human plasma Taylor and his collaborators^{13,17,18} have secured certain coagulating globulins, and other constituents of blood having clotting properties have been noted by Glazko and Greenberg⁴ and Bendien and Van Creveld.² No comparison of these preparations with our rabbit clotting globulin has been made.

Hess^{5a,b} writing about the injection of horse serum in intractable

hemorrhage pointed out that the same acceleration of coagulation could be achieved by injection of the purified euglobulin fraction instead of whole serum. The author obtained the euglobulin fraction from human, horse and sheep plasma by fractionation with ammonium sulphate. The concentration of ammonium sulphate that he used for precipitation of euglobulin corresponds to that by which we obtained our fraction *I-W* from rabbit's plasma. He claimed a favorable clinical effect of such an injection. However, the tables given in this paper on experiments carried out *in vitro* revealed quite a low clotting capacity of his euglobulin fraction.

Our observations on fraction *II-W* have naturally suggested the use of this fraction as a hemostat. Work is now in progress on a study of the value of this preparation as compared with other hemostatic agents which have recently been reviewed by Aggeler and Lucia^{1a,b} and Ferguson.³

Conclusions. 1. A description is given of a globulin fraction, isolated from rabbit plasma which possesses the property of clotting plasma.

2. It has been found that the "toxicity" of this fraction on intravenous injection is due to intravascular clotting.

3. Clotting globulin could be separated from that fraction of rabbit plasma which contains the major portion of the immune bodies.

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THE THROMBIC ACTIVITY OF A GLOBULIN FRACTION DERIVED FROM RABBIT PLASMA.

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PARFENTJEV has reported^{9a} that a globulin which possesses the property of coagulating citrated blood may be obtained by the fractionation of the proteins of rabbit plasma with ammonium sulphate. The present communication presents evidence confirming this observation and attempts to identify this clot-promoting factor in the light of modern knowledge of blood coagulation. In the accompanying paper⁷ certain practical clinical applications of this material will be presented.

Experimental. Methods. Rabbit plasma was obtained through the courtesy of the Lederle Laboratories and fractionations were carried out as suggested by Parfentjev^{9a,b}. Occasionally slight modifications in the procedure were made for purposes of comparison and quantitation.

Five hundred milliliters of rabbit plasma* obtained from rabbit whole blood containing as an anticoagulant 2.5% sodium citrate, were diluted with an equal volume of 0.9% sodium chloride solution. To 1 liter of the diluted plasma, 200 gm. of Merck's anhydrous ammonium sulphate were added and the pH of the mixture was adjusted to 7.4 (using phenol red indicator) with 1 N. sodium hydroxide. The mixture was then stirred mechanically at 37.5° C. for 16 to 18 hours. The resulting precipitate of plasma protein was removed by filtration. The filtrate was retained.

The precipitate was removed from the filter paper and redissolved in 500 ml. of 0.9% sodium chloride solution. To this, 100 gm. of ammonium sulphate were added. The pH was again adjusted to 7.4. The mixture was stirred at 37.5° C. for from 3 to 4 hours and filtered. The filtrate was combined with that from the first precipitation. The precipitate was again redissolved and the procedure of reprecipitation carried out as before. The final precipitate was discarded.

The filtrates from the three precipitations were pooled and the volume was measured. Sufficient anhydrous ammonium sulphate was added to raise the concentration of this salt to 30%. The pH was adjusted to 7.4. The mixture was allowed to stand at room temperature for 72 hours. During this time the precipitate settled out completely. The supernatant

* The Lederle Laboratories, Inc., have advised us that the plasma as received by us contains approximately an equal volume of 2.5% sodium citrate as the anticoagulant solution.

fluid was removed as completely as possible by syphonage and the remaining small amount by filtration.

The precipitate was removed from the paper and dissolved in a volume of 0.9% sodium chloride solution equal to one-tenth of the previous large volume. Thirty grams of anhydrous ammonium sulphate were added for each 100 ml. of sodium chloride solution used, and the pH was adjusted to 7.4. The mixture was stirred at 37.5° C. for from 4 to 5 hours and filtered. The filtrate was discarded. The precipitate was removed from the paper and dissolved in the minimum amount of distilled water necessary to effect solution. This was transferred to cellophane sacks and dialyzed against running tap water at approximately 7° C. for 48 hours.

The contents of the cellophane sacks were transferred to weighed serum bottles and dried by the lyophile method.⁴ The yields of dried material from 500 ml. of rabbit plasma ranged from 200 to 1400 mg. For purposes of quantitation the dried contents of the serum bottles were taken up into sufficient amounts of 0.9% sodium chloride solution to give it a concentration of total solids of 12%.

Certain modifications in the procedure were occasionally made for various reasons as indicated below.

Thrombic Activity of Rabbit Pseudoglobulin. Parfentjev has reported that his preparation of pseudoglobulin coagulated citrated blood. An attempt was therefore made to study the precipitation of fibrinogen by this material quantitatively. In the following experiments a 1:100 dilution of the sodium chloride solution of the rabbit globulin fraction was employed. Citrated normal human plasma was used as a source of fibrinogen in all experiments. In most of these 1 ml. of plasma was pipetted into each of a series of beakers and diluted with 30 ml. of 0.9% sodium chloride solution. Occasionally the amount of plasma was doubled when more fibrinogen was required for the experiment. The fibrinogen content of the plasma was determined in one sample by a method of recalcification.³ To the remaining samples of diluted plasma, varying amounts of the diluted pseudoglobulin preparation were added and the amount of fibrinogen, precipitated as fibrin, was determined. This determination was made both by the method of nitrogen difference and also by the direct determination of the nitrogen of the precipitated fibrin.³

For purposes of comparison the amount of nitrogen in each pseudoglobulin preparation was determined and the number of milligrams of fibrinogen converted to fibrin was plotted against the amount of globulin nitrogen added.

Table 1 shows the quantitative data from one such experiment. Comparable data were obtained on 8 other preparations of rabbit pseudoglobulin. These are shown graphically in Chart 1.

TABLE 1.—THE RELATIONSHIP OF RABBIT THROMBIN NITROGEN TO THE AMOUNT OF FIBRINOGEN CONVERTED TO FIBRIN FROM 1 ML. OF CITRATED NORMAL HUMAN PLASMA.

Mg. rabbit thrombin nitrogen added to plasma.	Mg. fibrin precipitated.
0.01	1.54
0.02	1.89
0.03	2.25
Total fibrinogen present in plasma as determined by recalcification	2.23

Since citrated plasma was used as a source of fibrinogen in these experiments, the precipitation of the fibrinogen might have been attributed to one of two possible reactions. If the preparation of rabbit pseudoglobulin contained sufficient calcium, then any thromboplastin in the preparation acting by releasing thrombin from the prothrombin of the plasma, could cause conversion of fibrinogen

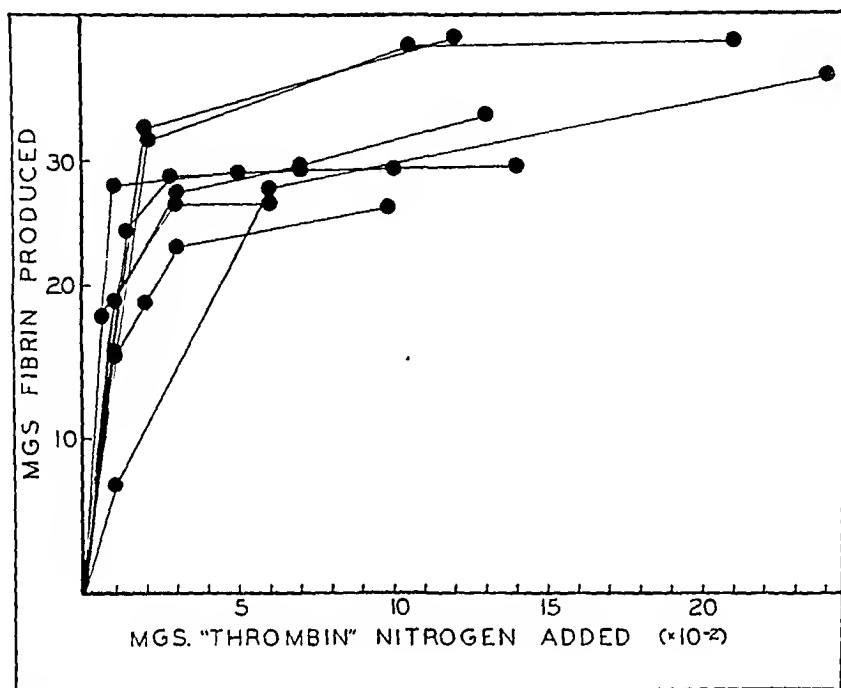


CHART 1.—The quantitative relationship of the amount of plasma fibrinogen converted to fibrin to the amount of rabbit thrombin added.

to fibrin. Or this conversion might have been the result of the direct action of thrombin independently of the other factors in the blood coagulation reaction. The calcium content of the various pseudoglobulin preparations was determined by a modification of the method of Fiske and Subbarow and related to their nitrogen content. As will be observed from the data presented in Table 2,

TABLE 2.—THE RELATIONSHIP OF CALCIUM TO NITROGEN CONTENT OF VARIOUS PREPARATIONS OF RABBIT THROMBIN.

Preparation No.	Mg. nitrogen per gm. of total solids.	Mg. calcium per gm. of total solids.
1	92	1.06
2	103	0.51
3	107	1.14
4	111	0.49
5	119	0.69
6	118	0.79
7	112	0.94
8	120	0.36

all the preparations contained small amounts of calcium which apparently were carried through the entire procedure. In no instance, however, did any of the preparations contain sufficient calcium to initiate coagulation. For example, on the basis of the data of Table 2, the largest amount of calcium added to the 1 ml. of plasma in the series of observations presented in Table 1, was 0.0001 mg., which could have had no effect on the conversion of fibrinogen to fibrin in 1 ml. of citrated plasma.

It would appear from an examination of the procedure that the clotting activity of the rabbit plasma was associated with the pseudoglobulin fraction. In view of the fact that the thromboplastic activity of human plasma has been shown to reside almost wholly in the euglobulin fraction,^{6,10} observations were made on rabbit plasma following the removal of euglobulin by dialysis of the plasma against cold running tap water for 8 days. Following this dialysis the rabbit euglobulin was found to resemble that from human plasma in that it contained almost all the coagulant activity of the plasma for hemophilic blood. Yet, when the remaining plasma proteins were treated with 30% ammonium sulphate and the latter part of Parfentjev's procedure carried out, a pseudoglobulin could be prepared which clotted citrated plasma. These data are presented in Table 3. This evidence indicates therefore that the clot-promoting substance in rabbit pseudoglobulin is neither calcium nor thromboplastin nor both calcium and thromboplastin. By definition therefore the clotting activity of rabbit pseudoglobulin must be the result of true thrombin and hereafter this rabbit fraction shall be referred as "*rabbit thrombin*." Such a conclusion is further justified by observations that the material is active both in the presence of large excesses of citrate or oxalate in the plasma after prothrombin is removed from the plasma by adsorption, and on fibrinogen solutions.

TABLE 3.—THE EFFECT OF REMOVAL OF EUGLOBULIN BY PRELIMINARY DIALYSIS ON THE ACTIVITY OF RABBIT THROMBIN.

Method.	Mg. thrombin nitrogen added to plasma.	Mg. fibrin precipitated.
Standard procedure	0.07	1.90
	0.13	2.18
	0.26	2.16
	0.66	2.45
Preliminary dialysis	0.06	0.98
	0.25	2.43
	0.69	2.91

The Preparation of Stable Dried Rabbit Thrombin. There is some evidence^{9b} that rabbit thrombin in solution is reasonably stable compared with solutions of other preparations of thrombin made in this laboratory. In the course of several months the activity was found to diminish to the extent of 10%. However, for practical

reasons the preparation of a dry stable powder was necessary. Two methods were employed for this type of preparation. The final solution of rabbit thrombin was lyophilized or precipitated by acetone and the acetone precipitate dried *in vacuo*. The data presented in Table 4 indicate that when either procedure was followed there was no loss of thrombic activity.

TABLE 4.—THE EFFECT OF DRYING RABBIT THROMBIN BY LYOPHILIZATION AND ACETONE PRECIPITATION ON THE THROMBIC ACTIVITY.

Method of drying.	Mg. thrombin nitrogen added to plasma.	Mg. fibrin precipitated.
None—control solution	0 010	1 54
	0 019	1 89
	0 040	2 25
	0 100	2 51
Dried by lyophile method redissolved in 0.9% NaCl solution	0 010	1 77
	0 018	2 13
	0 040	2 39
	0 090	2 52
	0 180	2 66
Precipitated by acetone, dried <i>in vacuo</i> —redissolved in 0.9% NaCl solution	0 010	1 34
	0 014	1 88
	0 029	2 29
	0 070	2 48
	0 140	2 71

Purification of Rabbit Thrombin. Parfentjev has indicated⁹⁶ that his material may be further purified by subjecting the final solution of the pseudoglobulins to an isoelectric precipitation at pH 5.2. Therefore a preparation made by Parfentjev was compared quantitatively before and after such purification. The data are presented in Table 5. It will be observed that the isoelectric precipitate contains somewhat more thrombic activity per milligram of thrombin nitrogen than the preparation not so purified. It is debatable whether there would be any advantage in carrying through this isoelectric precipitation for material to be used in the clinic as a hemostatic. However it is of interest since it removes much of the inert nitrogenous constituents of the rabbit thrombin solution, giving a purer product for purposes of investigation.

TABLE 5.—EFFECT OF ISOELECTRIC PRECIPITATION AT pH 5.2 ON THE ACTIVITY OF RABBIT THROMBIN.

Preparation.	Mg. thrombin nitrogen added to plasma.	Mg. fibrin precipitated.
Standard procedure	0 010	1 5
	0 020	1 9
	0 040	2 3
	0.100	2 5
Isoelectric precipitation	0 003	0 6
	0 007	2 5
	0.014	2 7
	0 030	3 2
	0.040	3 2

Thermolability of Rabbit Thrombin. As will be observed from Chart 2, the solution of rabbit thrombin is thermolabile. It is less so, however, than preparations of thromboplastin. Preliminary experiments indicate that when *absolutely dry* powdered rabbit thrombin is heated in sealed containers to temperatures of 110°C . for purposes of sterilization, there is little loss of potency. However, the presence of even small amounts of water in the material results in the destruction of the activity of the thrombin when it is exposed to these high temperatures.

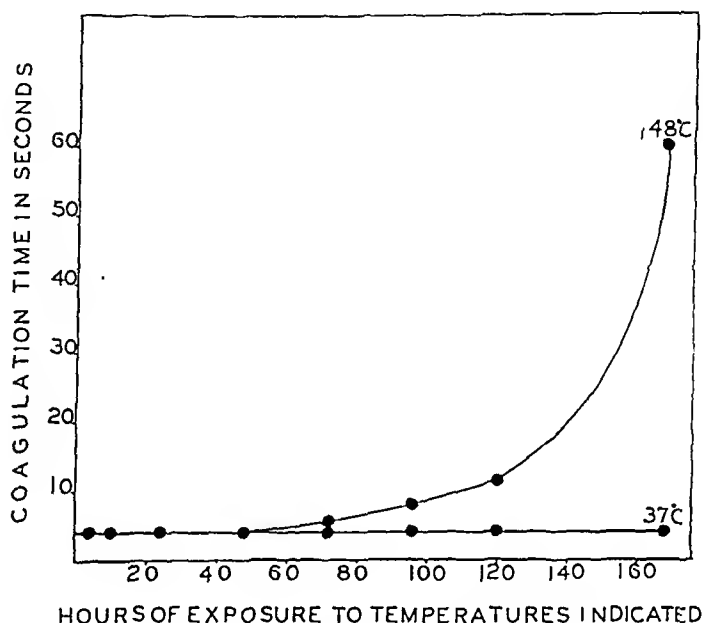


CHART 2.—The effect of temperature on the potency of rabbit thrombin. (0.1 ml. of a 1 to 10 dilution of rabbit thrombin added to 0.1 ml. of normal human plasma. Each test repeated at the time intervals shown.)

A Comparison of Rabbit Thrombin With Thrombins of Other Origin. In order to compare rabbit thrombin and thrombin prepared by other methods with regard to their action on fibrinogen of plasma, a series of quantitative experiments were performed. Thrombin prepared by the method of Seegers *et al.*¹¹ and by the conversion of prothrombin by rabbit brain thromboplastin in the presence of calcium were used in these studies. The data obtained on these studies are presented in Table 6. It will be observed that the action of rabbit thrombin is entirely comparable to that of thrombin prepared by these other methods.

Discussion. Thrombin by definition is a substance or a physiological activity, capable of directly converting fibrinogen to fibrin without the necessity of calling into operation calcium, prothrombin

and thromboplastin. It is therefore, to say the least, surprising that one may obtain directly from citrated rabbit plasma a substance possessing true thrombic activity. The observations recorded in this communication indicate quite clearly that when rabbit plasma is treated with certain salting-out procedures a pseudoglobulin may be obtained which does indeed possess thrombic activity. However, it must be remembered that at present we can offer no evidence that this thrombic activity is not due to changes in plasma proteins produced by manipulation involved in the procedure.

TABLE 6.—A COMPARISON OF RABBIT THROMBIN PREPARED BY PARFENTJEV'S METHOD WITH THROMBIN PREPARED BY THE DIRECT CONVERSION OF PROTHROMBIN OF STEER BLOOD, BY THROMBOPLASTIN IN THE PRESENCE OF CALCIUM.

Preparation.	Method.	Mg. thrombin nitrogen added to plasma.	Mg. fibrin precipitated.
Seegers <i>et al.</i> ¹¹	Prothrombin of steer	0 0600	0 45
	blood + steer lung	0 1900	1 51
	thromboplastin	0 3100	4 05
Seegers <i>et al.</i> ¹¹	Prothrombin of steer	0 0015	2 42
	blood + steer lung	0 0300	4 34
	thromboplastin	0 0900	4 76
Lozner, Adams and Taylor (unpublished)	Prothrombin of steer	0 0005	2 10
	blood + rabbit brain	0 0009	2 60
	thromboplastin	0 0018	4 08
		0 0090	5 54
Lozner, Adams and Taylor (unpublished)	Steer globulin substance	0 0008	1 64
	+ rabbit brain throm-	0 0010	1 57
	boplastin	0 0060	1 63
		0 0170	2 44
Parfentjev	Pseudoglobulin of rabbit	0 0100	1 54
	plasma	0 0200	1 89
		0 0400	2 25
		0 1000	2 51
Parfentjev	Pseudoglobulin of rabbit	0 0030	0 58
	plasma isoelectric pre-	0 0070	2 46
	cipitation	0 0100	2 72
		0 0300	3 18
		0 0400	3 24

Should thrombin exist preformed in rabbit plasma *in vivo*, obviously the presence in rabbit plasma of a substance capable of neutralizing it *in vivo* must be predicated. To account for the possible occurrence of thrombin in rabbit plasma several facts may be considered. It is conceivable that slow conversion of prothrombin to thrombin occurs. This is suggested indirectly both by the rapid disappearance of prothrombin from citrated rabbit, human and steer plasma and the frequent observation that small amounts of fibrin separate from citrated or oxalated plasma on standing. This phenomenon has been commented on by other authors.^{2,8} It is also of importance to consider the species of animal plasma involved in the present observations. It is well known that rabbit blood has a remarkably short coagulation time. It is also noteworthy that the thromboplastic activity of rabbit brain extract is much greater than that of similar extracts from steer, sheep or human brains.¹²

That this enhanced thromboplastic titer is shared by other rabbit tissues is a distinct probability. Should rabbit plasma have an increased thromboplastic titer, the conversion of prothrombin to thrombin would probably be accelerated.

There is some evidence of a preliminary nature¹ that while the potency of rabbit thrombin is not increased by the age of the plasma the total yield of thrombin appears to be increased.

The euglobulin fraction of plasmas of various species of animals has been shown to contain clot-promoting activity for hemophilic blood.^{6,10} We have called this clot-promoting substance or activity "globulin substance,"¹⁰ and Howell has called it "plasma thromboplastin."⁵ The data presented in this paper indicate that after this euglobulin fraction was removed from rabbit plasma by dialysis for 8 days, the supernatant fluid when treated by Parfentjev's procedure yielded a pseudoglobulin having unimpaired thrombic activity. This observation seems to differentiate "globulin substance" or "plasma thromboplastin" from rabbit thrombin, however here also one must reserve the possibility of protein change due to the subsequent salting-out procedure. Further differentiation is seen in the fact that the euglobulin fraction containing the thromboplastin factor requires both calcium and prothrombin to be present before fibrinogen can be precipitated from normal plasma. The pseudoglobulin fraction containing rabbit thrombin on the other hand can act on fibrinogen directly, in plasmas containing an excess of citrate or oxalate and also on plasmas from which the prothrombin has been removed by adsorption.

The amount of calcium present in rabbit thrombin is too small to initiate blood coagulation in the presence of citrate or oxalate. However, we have not as yet been able to prepare by any method a thrombic substance which does not contain this small amount of calcium which is apparently closely associated with the protein of the preparation.¹

Solutions of rabbit thrombin in sterile form are quite stable, compared with solutions of thrombin prepared by other methods. Some of the preparations used in these studies were 7 months old and still possessed marked activity. The thermolability of rabbit thrombin is fairly low. Absolutely dry rabbit thrombin may be sterilized in sealed containers at 110° C. The low thermolability also permits the drying under reduced pressure of gauze and similar material impregnated with solutions of rabbit globulin.

A completely stable dry powdered preparation may be obtained by the method of vacuum drying at low temperatures such as is used in the lyophile process or by precipitation of the pseudoglobulin from its final solution with acetone and subsequent drying *in vacuo*. Both preparations are of equal activity, and show no loss of potency as compared to the original pseudoglobulin solution from which they were derived. The high potency, ease of prepara-

tion and high yield of rabbit thrombin would clearly indicate the desirability of clinical trial of the material as a hemostatic. Certain observations concerning the use of rabbit thrombin in the control of hemorrhage are presented in the following paper.

Conclusions. 1. The observation of Parfentjev that rabbit plasma contains a substance or physiologic activity capable of converting fibrinogen to fibrin is confirmed.

2. Parfentjev's material is apparently a pseudoglobulin which possesses true thrombic activity.

3. It may be differentiated from thromboplastin by its manner of preparation and its independence of calcium-ion concentration in its action on fibrinogen.

4. Methods of preparing the material in a stable powdered form are presented.

A material has been prepared from the plasma of steer by the procedure outlined in this paper possessing similar properties to that obtained from rabbit plasma.

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THE USE OF RABBIT THROMBIN AS A LOCAL HEMOSTATIC.

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THE body possesses two main defenses against hemorrhage, the coagulation of the shed blood and the mechanical behavior of blood vessels toward injury. Thrombin precipitates fibrin instantaneously.

independently of the other factors in the blood coagulation reaction, and thus can be of value in aiding local hemostasis. It has been used therapeutically in this manner with encouraging results.^{4,6} The preparation of this physiologic complex however has in the past been difficult and time-consuming and only small yields were obtained from relatively large amounts of plasma. Increased availability has been achieved because of the isolation by Parfentjev, from rabbit plasma, of a globulin fraction able to clot citrated blood.² This fraction has been identified by this laboratory as possessing great thrombic activity. The details of this identification are presented in the preceding paper.⁵ Translating the results into practical terms, one part of dry powdered rabbit thrombin will clot 60,000 parts of 0.25% citrated blood within three seconds. The potency of the material, the shortness of the time necessary for *in vitro* clotting, the simplicity of preparation and large yields, made it desirable that the hemostatic properties of rabbit thrombin be investigated clinically. This communication reports the results of these investigations.

Methods. Three types of preparations of rabbit thrombin were used, a saline solution containing from 10 to 12% total solids, a dry sterile powder prepared by lyophilization and a dry sterile powder prepared by acetone precipitation and subsequent *in vacuo* desiccation. Some of the materials used were prepared in this laboratory, others were furnished by Dr. Parfentjev. With these preparations, two types of investigations were undertaken; a controlled study of hemostasis following a standard trauma in normal subjects and observations on the use of rabbit thrombin in the control of bleeding from small wounds in patients with and without hemorrhagic diseases.

Controlled Study of Hemostasis in Normal Subjects. A standard trauma was utilized in order to study hemostasis in the normal subject. For this purpose a modification of the Ivy bleeding time¹ was used. A sphygmomanometer cuff was placed around the upper arm of the subject and inflated to 50 mm. Hg pressure. A wound with an ordinary mechanical lancet was then made on the ulnar side of the flexor surface of the forearm, avoiding visible veins, approximately 3 mm. in width and 4 mm. in depth which produced bleeding lasting from 5 to 7 minutes when not treated. The amount of bleeding was measured by gently approximating a square of filter paper to the drop of blood over the wound at 30-second intervals. When the bleeding stopped, the time was recorded and the areas of the drops of blood on the filter papers were measured and totalled. Four methods of treatment with rabbit thrombin were investigated. Controls were repeated in identical fashion except for the omission of rabbit thrombin.

The details of the four methods of treatment are as follows:

I. "**Wet Spray:**" The wound was allowed to bleed for 60 seconds and was then sprayed with the solution of rabbit thrombin for 15 seconds using a "nebulizer." Following this procedure the amount of bleeding was determined as described above.

II. "**Dry Spray:**" Dry powdered rabbit thrombin was applied to the wound in identical fashion to that described for the solution.

III. "**Wet Application:**" Immediately following the trauma a square of filter paper moist with the solution of rabbit thrombin was applied to the wound. This was kept in apposition to the wound without pressure for

2 minutes. The amount of bleeding following this was measured and added to the amount of bleeding on the filter paper used in the treatment. For the controls to these observations a square of filter paper moist with saline was applied in an identical fashion.

IV. "Dry Application." This procedure was identical with that used for the application of the solution of rabbit thrombin except that the square of filter paper applied to the wound was dampened with saline and sprinkled with a small amount of dry rabbit thrombin.

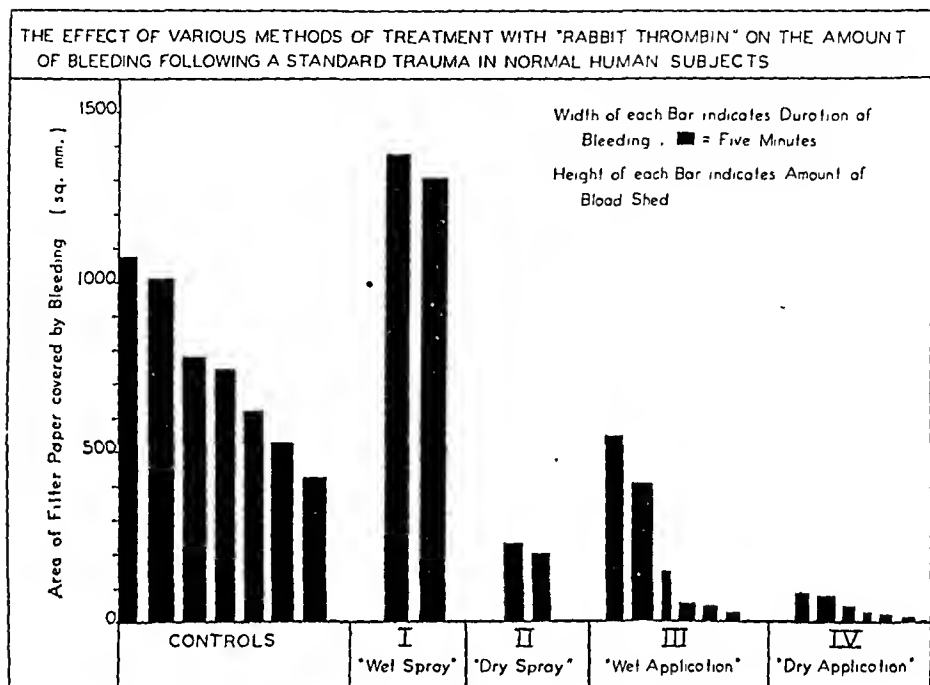


CHART 1.

Results. The results of this study are presented in graphic form in Chart 1. It will be observed that all methods of treatment except that of the "Wet Spray" considerably decreased the amount of bleeding. The most effective method was that of "Dry Application." In general, the dry powdered rabbit thrombin gave better results than the solution. The apparent prolongation of bleeding produced by the "Wet Spray" was the result of the instantaneous formation of a flimsy clot which, however, did not adhere to the wound and beneath which the bleeding continued.

Observations on the Use of Rabbit Thrombin in the Control of Bleeding in Patients. Observations were carried out on 11 patients who were bleeding from *small wounds*. Nine of these had hemorrhagic diatheses, 4 with hemophilia, 3 with symptomatic thrombocytopenic purpura, 1 with hypoprothrombinemia and 1 with hereditary thrombasthenia. The other 2 patients had hypertension with epistaxis. Dry powdered rabbit thrombin was usually used and the technique of application was in general comparable with that pre-

vously described.³ Essentially this consists of impregnating with the dry powder a dressing, pack or "gauze bite" which has been dampened with sterile saline. This impregnation is carried out in such a fashion as to allow the dry powder to come into immediate contact with the bleeding surface.

TABLE 1.—SUMMARY OF OBSERVATIONS ON THE USE OF RABBIT THROMBIN AS A LOCAL HEMOSTATIC IN 13 PATIENTS.

Pt. No.	Obs. No.	Age (yrs.)	Diagnosis.	Bleeding site.	Method of treatment.	Duration of hemorrhage prior to institution of rabbit thrombin treatment (days).	Degree of hemostasis.
1	1	28	Hemophilia	2.5 cm. laceration on hand	10% solution on dressing	4	Complete
2	2	36	Hemophilia	0.6 cm. laceration in antecubital vein	Powder on dressing	...	Complete
3	3	7	Symptomatic thrombocytopenic purpura (acute leukemia)	Sternal biopsy	Powder on dressing	1	Complete
4	4	23	Hemophilia	Gum	Powder on "gauze bite"	5	Complete
5	5	22	Hemophilia	Tooth socket	Powder on "gauze bite"	"	Complete†
5	6	22	Hemophilia	2 tooth sockets	Powder on "gauze bite"	"	Complete‡
6	7	24	Symptomatic thrombocytopenic purpura (aplastic anemia)	Stab wound in hemarthrosis	Powder on dressing	2	Complete
7	8	46	Symptomatic thrombocytopenic purpura (aplastic anemia)	Nose	Powder on pack	1	Partial once Complete twice
8	9	41	Hypertension	Nose	Powder on pack	14	Complete
9	10	52	Hypertension	Nose	Powder on pack	5	Complete
10	11	48	Hypoprothrombinemia (non-tropical spurge)	Nose	Powder on pack	1	Complete
11	12	33	Hereditary thrombasthenia	Tooth socket	Powder on "gauze bite"	2	Complete
2	13	36	Hemophilia	Tooth socket	Powder on "gauze bite"	"	Complete§

* In these patients rabbit thrombin was used immediately following the trauma.

† "Bite" changed every 24 hours, socket healed in 8 days.

‡ "Bite" changed every 24 hours, socket healed in 7 days.

§ "Bite" changed every 24 hours, socket healed in 4 days.

For purposes of brevity the clinical observations have been summarized in Table 1. With only one exception (Patient 8), the details of which are presented below, the hemostasis produced by rabbit thrombin was complete and immediate. That is to say, as soon as the dressing, pack, or "gauze bite" containing rabbit thrombin was applied to the bleeding surface, arrest of hemorrhage immediately occurred. Prior to the application of rabbit thrombin in these patients, hemorrhage had occurred for varying lengths of time. In 9 of the 11 patients this hemorrhage had not been controlled by various hemostatics, including pressure bandaging, and application or tamponage with adrenalin, ferric subsulphate solution and animal muscle. In one (Patient 9) with hypertension and epistaxis, bleeding had persisted for 14 days prior to rabbit thrombin

therapy despite all the above measures and four transfusions of blood.

In Patient 8, mentioned above, in which hemostasis on the first application of rabbit thrombin was only partial, the diagnosis was symptomatic thrombocytopenic purpura associated with aplastic anemia. Two subsequent applications on following days produced complete and immediate hemostasis. The unsatisfactory result on the first application was probably due to the failure of the operator to bring the rabbit thrombin into immediate contact with the bleeding site.

The dry powder was employed in the majority of patients exclusively. However, isolated observations carried out with rabbit thrombin solution indicated that it, too, was of value as a local hemostatic, but perhaps not quite as effective as the dry powder. No toxic effects from the application of rabbit thrombin were observed in any of the normal subjects or patients, no matter in what form it was applied.

Discussion. The above observations indicate that rabbit thrombin is of distinct value as a local hemostatic in small wounds. This apparently results from the property of this material very rapidly to precipitate fibrin and thus close the wound.

Numerous practical methods for the application of rabbit thrombin suggest themselves. Such methods, however, undoubtedly will depend on the location of the bleeding site and the personal choice of the surgeon. Gauze bandages impregnated with thrombin would seem to be likely of success in controlling bleeding from wounds on the extremities. It is important that the particular method employed be one in which the highest concentration of rabbit thrombin comes into contact with the bleeding surfaces. In many situations this is more feasible with the dry powder than with a solution.

It should not be forgotten that in addition to the factor of coagulation of blood when shed, the factor of vascular defense is important in determining the duration of bleeding. Certain situations occur where the blood vessel factor fails to such an extent that no hemostatic which depends for its action on the formation of fibrin can be effective.

It must also be borne in mind that the parenteral administration of thrombin is very toxic and may result in generalized thrombosis. It is important therefore that the material be used cautiously.

Summary and Conclusions. 1. Observations are reported indicating that rabbit thrombin is of distinct value in the control of hemorrhage from *small wounds* induced by a standard trauma in normal persons and in 9 patients with and 2 without hemorrhagic diatheses bleeding spontaneously from small wounds.

2. The material apparently accomplishes its results by the instantaneous precipitation of fibrin.

3. No toxic manifestations were observed following the application of rabbit thrombin to the small wounds.

4. It would appear desirable that these observations concerning the use of rabbit thrombin as a local hemostatic be extended.

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PROGRESS OF MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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NASAL PHYSIOLOGY.

It is only within recent years that the interest of rhinologists has been drawn to the much neglected field of nasal physiology. Previously rhinologists centered their energies on anatomy, surgical anatomy—and more recently—on pathologic anatomy. The result has been a period of satisfactory growth. With the recognition of the importance of the functional point of view in rhinology, it is quite conceivable that nasal physiology will bloom into deserving maturity. The importance of knowing how a nose works is stressed by Proetz,¹⁰ who deplors the small amount of space given in standard textbooks and monographs to nasal physiology. There are many pitfalls that may beset the rhinologic surgeon unless he studies the functional viewpoint. For old methods, old drugs and old operations should be abandoned when they have been discredited.

Frenckner and Richtner⁴ report a study of ciliary movements in living and anatomic sections under normal and pathologic conditions. The beating frequency of the cilia was found to vary between 160 and 250 beats per minute under normal conditions. Repeated infections of the nasopharynx seemed to arrest ciliary activity. Ethyl chloride had a certain resting effect, but ether narcosis and injection narcosis with pernocton and urethane seemed to be innocuous. Certain local anesthetics checked the ciliary activity, at least temporarily. Experiments on animals appear to show that a long hypovitaminosis with regard to vitamins A, C and D causes slowing of the ciliary activity but that a short, complete avitaminosis does not have any obvious effect. No change in ciliary activity was caused by administration of hormones. Anatomic sections immersed in Ringer's solution showed no inhibition of ciliary activity for a period of 6 to 10 hours. In physiologic salt

solution the frequency of the ciliary beats was visibly lessened somewhat earlier. Weak solutions of ephedrine had a slightly stimulating effect. At no time was complete inhibition observed. Dilute solutions of adrenalin had an inhibitory effect on mucous membrane sections, but the ordinary 1-1000 solution had no visible effect on mucous membrane of living animals. Weak colloidal silver preparations appeared innocuous, while ephedrine solution combined with 5% neoprontosil solution had a stimulating effect. Prontosil injected into living guinea-pigs produced no visible change in ciliary activity. As a general rule, expectorants and volatile oils, applied locally or in the form of vapor, produced slowing of ciliary activity following a brief period of stimulation. The inhibitory effect produced by many of the agents was found to be less pronounced in the mucous membrane of a living person than in extirpated mucous membrane sections. Leasure⁷ emphasizes the importance of the thin sheet of mucus which covers the mucous membrane of the respiratory tract. The mucous membrane of the respiratory tract, especially that of the nasal portion, needs active cilia moving a sheet of mucus in order to be healthy. At times perfectly healthy nasal mucous membrane is quite capable of resisting the most virulent invader. Any inhibition of the production of mucus constitutes an exposure. Secretory parasympathetic innervation to the nasal mucous glands has been reported. A predominant activity of the sympathetic nervous system is found to coincide with circumstances associated with common exposures to cold.

In their study of the effect of estrogens on ciliated mucosa, Boyd and his associates¹ reveal that cilia of the bucco-esophageal mucosa of the frog are most sensitive to estradiol and least sensitive to estrone and that the sensitivity to estriol lies midway between. In minute amounts, too small to affect the hydrogen-ion concentration or the electrolyte concentration, these estrogens first stimulate and then, in larger doses, depress ciliary movement. If the value of 1 is given to the stimulating power of estrone toward ciliary movement, then estriol may be calculated to be twenty times as active as estrone and estradiol one hundred times as active. This order of activity toward cilia does not correspond to the order of estrogenic activity of these crystalline substances. If estrone is given an estrogenic activity of 1, estriol may be estimated as one one-hundredth as active and estradiol as ten times as active as estrone. Since cilia form an integral part of the protoplasm of the mucosal cells, the order of activity of estrogens on ciliary movement may reflect a corresponding order of activity on other functions of mucosal protoplasm. Among these other activities, the authors were especially interested in the power of estrogens to relieve azena and atrophic rhinitis, which has been reported by other investigators. If the present data have any application to the latter studies, they indicate that dosage is an extremely important factor. Nash⁸ declares that the function of a mucous membrane is to produce mucus, but the nasal mucous membrane must produce mucus within certain quantitative limits if the nasal functions are to be maintained perfectly. Any shifting of this mucus production into either a hypofunction or a hyperfunction will result in a functional nasal disturbance, and the signs and symptoms of this disturbance will depend upon the amount and character of the dysfunction and the length of time it has continued.

A normally functioning nasal mucous membrane produces a limited amount of mucus. It does not hypofunction nor does it hyperfunction. Hypofunctional diseases, such as atropine rhinitis, physical rhinitis, psychic rhinitis, atrophic rhinitis, febrile rhinitis and debilitative rhinitis, begin with dryness of the mucous membrane, and if long continued terminate in atrophy. Hyperfunctioning diseases, such as irritative rhinitis, infective rhinitis, allergic rhinitis and the rhinitides produced physically, psychically and by food and the endocrines, begin with engorgement and rhinorrhea, and if long continued terminate in hyperplasia. Relatively few agents or conditions produce hypofunctioning diseases, but many produce hyperfunctioning diseases.

Fabricant,^{3a-c} in receiving the Casselberry Prize Award of the American Laryngological Association for 1941, stressed the significance of the pH factor as a basis for the treatment of upper respiratory infection. With the advent of comparatively new and simple methods for measuring hydrogen-ion concentration, it is possible to awaken the clinician's interest in a type of investigation that has practical application to innumerable and diversified fields. To offset the fact that nasal secretions, when collected, are susceptible to changes in pH almost instantly when they are exposed to air and are divorced from the normal milieu of the nose, the use of the glass electrode with its associated measuring equipment, the Coleman electrometer, has made it feasible to measure the pH of nasal secretions *in situ* with ease and precision. By conducting minute-to-minute readings of the pH values of nasal secretions in a group of patients observed daily for 2 years and graphically charting the results, it has been possible to explain adequately the wide range of nasal pH revealed in contributions elsewhere by workers employing other methods of procedure in studies of clinically normal nasal conditions and of acute rhinitis, acute rhinosinusitis and allergic rhinitis. The pH of nasal secretions *in situ* describes a series of high and low points. At no time does the pH remain constant over an appreciable period. Its fluctuations in a clinically normal nose—from approximately 5.5 to 6.5—appear to follow a definite course. The futility of relying on only one pH reading is amply illustrated by the frequent numerical changes in pH values that occur when readings are recorded over one hour or more. The course of nasal pH is altered by the application of either cold or heat. Cold produces a drift toward alkalinity, heat a drift toward acidity. The pH of nasal secretions *in situ* during an attack of acute rhinitis or acute rhinosinusitis or during the more active phases of an attack of allergic rhinitis is alkaline. This finding has clinical significance, for those nasal vasoconstrictors which can lower the nasal pH from an abnormal alkaline status to a normal slightly acid status—a pH level between approximately 5.5 and 6.5—may perform a valuable function. Conversely, those nasal vasoconstrictors which raise, enhance or perpetuate an alkaline nasal pH during these rhinologic conditions may prolong an undesirable status of nasal pH. Acceptable nasal therapy for acute rhinitis and acute rhino-sinusitis often includes the careful selection of an appropriate nasal vasoconstrictor, counseling the patient to obtain adequate rest and sleep, and the judicious administration of external heat for the relief of pain in selected cases of acute nasal sinusitis. Each of these well-recognized therapeutic measures

produces but a single, uniform nasal pH phenomenon—acidity. All elective nasal surgery procedures which require the use of topical anesthetics and vasoconstrictors are performed in a completely acid nasal pH environment. At this time the pH of the nasal secretions *in situ* is acid, the topical anesthetics themselves are acid, the vasoconstrictors are acid, and the noticeable effect of the topical anesthetics, alone or in combination with a few drops of a vasoconstrictor, is acid. The actual return of the nasal pH to an acid status is accomplished—unwittingly or no—by every physician who prescribes certain well recognized nasal vasoconstrictors. Should the occasional therapeutic nihilist omit the use of a nasal vasoconstrictor but, in turn, utilize such measures as adequate sleep and rest and external heat, singly or collectively, the end result can be only that of establishing an acid nasal pH. Fabricant suggests that every nasal vasoconstrictor available to the public should satisfy two basic physiologic requirements: 1, the restoration and maintenance of normal ciliary activity; and 2, the possession of a slightly acid pH value between 5.5 and 6.5. He also suggests that silver preparations be standardized to a similar level, for those silver preparations, nasal vasoconstrictors and antiseptics which either raise, enhance or perpetuate the alkaline nasal pH found in acute rhinitis and acute rhinosinusitis prolong an undesirable status of nasal pH—an alkaline status in which the bacteria accompanying the acute infection find a fertile field for growth. To divorce and separate the ciliary factor from the pH factor is to tell but half the story of applied nasal physiology.

Physiologic experiments prove that an inspiratory stream of air can be deflected and broken by the shape and position of the nasal aperture and also by any mechanical obstacle or alteration in the lateral and medial walls of the nose. The various structures which, if abnormal, can deflect these inspiratory air currents may be grouped under the general term "nares." According to Cinelli,^{2a,b} they are the columella and anterior portion of the nasal septum, the alar cartilages with lateral and medial crura, the upper lateral cartilages and the small constrictor-dilator muscles of the nose. Collapse of the nares may be either functional or organic. In the functional type, the structural tissue of the nose is normal, but the patient does not breathe correctly. "He breathes with the nose and not through the nose." The proper corrective measure is to have the patient, before a mirror, breathe in slowly, deeply and long, with the nares intentionally dilated outward. The organic type of collapse of the nares may be incomplete or complete. The incomplete collapse is due to a weakened or atrophic condition of the upper lateral cartilage. Correction is obtained by the implantation of cartilage with its attached outward perichondrium, which strengthens the middle third of the lateral wall, thereby giving sufficient mechanical support to prevent it from impinging toward the septum. The complete organic collapse is due not only to atrophy of the upper lateral and alar cartilages but chiefly to atrophy of the dilator and constrictor muscles of the nares. The nasal muscles play an important part in the physiology of the nose and in the physiognomy, character and personality; they are a source of emotional expression in the daily tasks and an understanding of their nature and function is of importance to persons engaged in the arts of painting and sculpture. To consider these muscles rudimentary would be to destroy man's weapon of individuality.

The correction of complete organic collapse of the nares is surgical. The nares are transfixed laterally in such a position that they cannot collapse. The result is immediate improvement in breathing.

The surgical establishment of nasal ventilation is discussed by Parkinson.⁹ He writes that inadequate nasal ventilation is a common and important problem. It is due to a variety of pathologic entities, the most usual being persistent congestion, persistent edema, deviated septum and mucosal hyperplasia. Many cases are relieved by allergic or endocrine control, or by nasal or sinusal treatment. The remaining causes can be relieved by intranasal surgery following sound and approved principles. As the causes of chronic obstruction vary, surgical measures must vary accordingly. Besides submucous resection, measures are outlined for resetting the inferior turbinate, reducing its erectile capacity, and removing portions that are hyperplastic. Intra-nasal antral windows are useful as additional space for resetting the inferior turbinate. This is recommended as a valuable addition to ventilation surgery. Improved ventilation brings improvement in nasal physiology. Hilding⁵ finds that rabbits develop suppurative sinusitis readily as a result of operative windows made between the maxillary sinus and the nasal cavity. Sinusitis is much more apt to occur if the window is made at or near the ostium than if it is made at a point distant from the ostium. A sinus may not be mutilated surgically with impunity in disregard of the physiology of the ciliary mechanism. Apparently, open windows, like scars, may disrupt sinus drainage if placed in positions where they interfere with ciliary flow. It is possible to make windows in such positions with reference to the ciliary mechanism that they do not seriously interfere with drainage. In a thoughtful discussion of the relationship of nasal obstruction to impairment of hearing, Johnson⁶ states that the presence of an anatomic obstruction in the nose cannot affect the eustachian tube either by misdirecting the air currents in the nasopharynx or by causing inflammatory reactions in the tube. If, on the other hand, this obstruction causes a prolongation of infections of the upper respiratory tract, so that they more frequently go on to sinusitis, it is likely that the presence of infections in the nose and in the nasopharynx would cause inflammatory reactions in the tube that might lead to adhesive processes in the middle ear. The inflammatory change, therefore, has been the result of the infection and not the direct result of the obstruction. The author reviews 46 cases of submucous resection for nasal obstruction. In 65 % (30 cases) there was either no deficiency in hearing or only high tonal dips. In the cases in which some improvement of hearing was present the audiometric improvement was not sufficient to warrant urging the operation as a means of improving hearing.

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DERMATOLOGY AND SYPHILOLOGY.

UNDER THE CHARGE OF

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THE TRIVALENT ARSENICALS IN SYPHILIS.

PART II. TREATMENT REACTIONS.

THIS review is a continuation of the discussion of the trivalent arsenicals in syphilis which we began in a previous issue of this Journal (AM. J. MED. SCI., 201, 611, 1941).

It is hardly necessary in a modern discussion of reaction to treatment with the antisyphilitic drugs to stress the importance of these reactions to the future of the syphilis program. It is obvious that the practising physician is ever seeking an arsenical preparation which will be both easy to administer, and when administered least incommoding to the patient, and at the same time, will produce the desired therapeutic effect. Although progress in this direction has been made recently (arsenoxide—Mapharsen), previous discussion has pointed out that the ideal has not yet been attained. Accordingly, it is still necessary for the physician to have a clear understanding of the types and significance of the various untoward reactions which he may encounter in the management of his patient with syphilis. It is not feasible in so short a review to give all the clinical data necessary for recognition of the various types of reaction. An attempt will be made, however, to analyze the various factors which may play a part in the production of these by-effects or arsenical medication. For purposes of discussion we have followed the classification of treatment reactions to the arsenicals, proposed by the Coöperative Clinical Group^{31a} as follows:

I. *Mild.*

- A. Gastro-intestinal reaction
- B. Nitritoid reaction
- C. Pruritus
- D. Slight skin eruptions
- E. Transient kidney irritability

II. *Severe.*

- A. Acute yellow atrophy of the liver
- B. Aplastic anemia
- C. Arsenical stomatitis
- D. Crustaceous dermatitis
- E. Icterus
- F. Ocular damage
- G. Purpura hæmorrhagica
- H. Venous embolus
- J. Death

This classification is not all-inclusive, but is sufficient for practical purposes.

Incidence. Relatively few large-scale or intensive studies of reaction to arsenicals have appeared in recent years. Waugh and Milovich¹⁷⁹ have recently reviewed severe reactions to arsphenamine; various papers on treatment reactions in the United States Navy have been collected by Lt. Com. Stephenson and his co-workers,^{33,149-151,152a,b} and reports by Ervin Epstein^{41d} on cutaneous reaction to Mapharsen; by Ireland,⁷³ the collected reviews by Cole and his associates,³⁰ and the Coöperative Clinical Group studies^{31a} on arsenical reactions are the principal American contributions. In evaluating published accounts of various reactions to the arsenicals, the degree of particularity with which the observer has collected his material must be considered. Certain individuals will record the slightest reaction as significant, and thereby include in their totals data which do not figure in the estimates of other observers. Others rate only serious reactions as worthy of statistical estimation. The mechanical processes of collecting and recording reactions to treatment with the arsenicals affect the statistical results. It follows that two observers equally competent, working in presumably equally ideal situations, come to widely differing conclusions from their data. The following account summarizes some of the factors that appear to affect the occurrence of reaction in the treatment of syphilis with the arsenicals.

Age, Sex, Race. The majority of reactions occur in the age groups in which intolerance of the drugs due to functional impairment of advancing years is to be expected. A partition of reaction incidence between youth and age was observed by the Coöperative Clinical Group^{31a} which found that there was an increased incidence of mild reaction in the age groups 15 to 19 and 20 to 24; consisting especially of gastro-intestinal and nitritoid reactions. As the age of the patient increased, mild reactions showed a tendency to decrease, but severe reactions tended to increase in frequency. This was especially true for crustaceous dermatitis (except in the 15 to 19 age group) and icterus, which rose from an incidence of 0.5% in the age group 15 to 19 to 1.6% in the age group 45 to 49. Classifying reactivity by type of syphilitic involvement present confirmed these findings. Cole and his associates³⁰ found that in older individuals treated with arsphenamine, more icterus was seen than among younger patients. Skin eruptive reactions were more frequent below 35; pruritus above 35. Nitritoid reactions were observed more frequently after this age. In contrast with the earlier Coöperative Clinical Group findings, severe crustaceous dermatitis was observed almost entirely before the age of 35. Hemorrhagic encephalitis was found by Cole and his associates³⁰ to occur more frequently in young adulthood. The Coöperative Clinical Group found that mild arsenical reactions were twice as frequent in females as in males in both colored and white races; while severe reactions were seen more frequently in whites without regard to sex. Cole and co-workers showed, furthermore, that white women are more reactive than negro women. Waugh and Milovich,¹⁷⁹ reporting the experience of the Hot Springs treatment center of the United States Public Health Service, found that there were 2.47 severe reactions per 1000 arsenical injections among the men, and 2.39 among the women. The incidence

was higher for white men than colored men, but was higher for colored women than for white women. The single case of acute yellow atrophy of the liver observed at Hot Springs occurred in a white man, and the single case of agranulocytopenia with angina occurred in a white woman with secondary syphilis. These observers found 1.83 ieterus rcactions per 1000 arsenical injections among the men, and 1.14 among the women; and no difference in the incidence of ieterus as between white and colored patients. Crustaceous exfoliative dermatitis was more than twice as common among women as among men; and about the same for the white and colored races. They found, furthermore, that this reaction was almost twice as common among white women as among white men, and four times more common among colored women than colored men. While the United States Naval statistics^{33, 149, 151, 152a, b} cannot be used for comparative purposes here, the generally accepted idea that women are more reactive than men may to some extent account for the low incidence of reaction in the Naval statistics which concern men, and young men at that. The rôle of pregnancy and other factors explaining the apparently increased incidence of treatment reactions to the arsenical in women will be presently discussed.

Rajam¹²² reported his experience with reactions and complications in the course of administration of 24,550 doses of neoarsphenamine to 7160 East Indians with syphilis. His statement that this race does not tolerate neoarsphenamine is well borne out by his figures; dermatitis was produced in 1 of each 126 patients treated, an incidence of 1 to 147 for men and 1 to 83 for women. The individual dose of neoarsphenamine never exceeded 0.3 gm., yet there was 1 case of dermatitis for each 431 injections; 1 to 514 for the men and 1 to 264 for the women. There were 3 deaths. Jaundice, however, was less than half as common, but in this series hemorrhagic encephalitis developed in 6 cases. In his masterly study of blood dyscrasias in the treatment of venereal diseases, the late E. T. Burke¹⁵ found that approximately 0.5% of women patients and 0.3% of male patients in his Whitechapel series (1934-38) developed blood dyscrasias. Burke found sulfarsphenamine to be the common factor in all of his cases, but does not state whether more men or more women were treated with this drug.

In connection with the effect of race, Sampson and Latven¹²⁶ showed that there is a definite and constant difference in the tolerance to neoarsphenamine of albino rats from different colonies or racial strains. It is apparent from their experiments that it is not possible to make a significant comparison of toxicity among samples of neoarsphenamine when rats from different strains are used.

Relation of Number of Treatments and of Dosage to the Frequency of Arsenical Complications. There is little doubt that patients may acquire extraordinary tolerance to the arsenicals, as exemplified by the remarkable case of Photinos,¹²⁰ in which a woman patient was given a total of 191 gm. of neoarsphenamine in 230 injections of which 190 were 0.9 gm. each, during a period of 6 years. As a general rule, the percentage of persons having reaction rises from the sixth to the tenth injection, and then remains more or less stationary up to the sixteenth to twentieth injections. From this point there is a further rise, which then declines to a low point between the thirty-first and the thirty-fifth injection. Harrison^{64b} and Cole and his co-workers²⁰ have both ob-

served severe reactions often from the seventh to the fifteenth dose. The Coöperative Clinical Group^{31a} found that reactions either of the mild or severe type occurred with the greatest frequency during the first course of treatment, and dropped off gradually with each succeeding course. Waugh and Milovich¹⁷⁹ found that 87% of the crustaceous dermatitis reactions occurred less than 2 months after the beginning of treatment. Twenty-two per cent followed 1 to 6 arsenical injections. In the Coöperative Clinical Group material 67% of the crustaceous dermatitis manifested itself before the second month of treatment; 53% following 1 to 6 injections, and 14% following 7 to 12 injections. In Waugh and Milovich's series, men received an average of 11 injections of arsphenamine and the women 13. Burke¹⁸ believed from his experience that postarsphenamine blood dyscrasia is unrelated to dosage but that it tends to appear late in the course of treatment. Our experience corresponds to that of Burke. It is probable that in this and some other types of reaction (*e. g.*, hepatic) subthreshold injury begins long before the symptomatic reaction appears and can be detected by appropriate tests (*e. g.*, blood smears and counts, icterus index).

Type of Syphilis and Incidence of Arsenical Reaction. The Coöperative Clinical Group^{31a} found that in early syphilis, the rate for mild reactions was 3 times higher than for severe reactions. Severe reactions, however, showed their highest incidence in primary syphilis followed by a lessened incidence in secondary and latent syphilis. Waugh and Milovich's¹⁷⁹ report showed the incidence of severe reactions to be about the same in all the earlier stages of syphilis; being 2.4 per 1000 arsenical injections for primary syphilis, 2.69 for secondary syphilis and 2.41 for latent syphilis. They also found that the incidence was considerably higher for the white patient with primary syphilis and slightly higher for white patients with secondary syphilis. In latent syphilis the incidence for the colored was slightly higher than that for the white patient. Cole and his associates,³⁰ in their attempt to determine whether the stage of syphilis during which the patient began treatment influenced the type of complication occurring, found that among the early cases the incidence of gastro-intestinal reactions was 27.7%, whereas among the latent cases the percentage was nearly doubled—50.6%. A much higher percentage of patients with early syphilis suffered slight skin reactions than of those who began treatment while in the latent stages. There were twice as many nitritoid reactions among the latent cases as among the early cases. Patients with treatment-resistant syphilis have been found to be specially reactive to the arsenicals by Jessner⁷⁶ and by Beerman.^{13c} This fact may be indirectly concerned in the production of treatment-resistance since a reacting patient can only be given smaller doses which in turn may produce treatment-resistance.

Effect of the Type of Arsenical Drug on Reaction. Excluding such factors in individual drugs as certain metallic elements (*e. g.*, silver in silver arsphenamine which may produce argyria,^{22a,121} there are a number of differences in the reaction tendencies of the various arsenical drugs. As in any of the factors discussed in this review, this one factor of drug type cannot be used in itself to explain the incidence of reactivity of a given group of patients to the arsenical. The experience of

the Coöperative Clinical Group^{31a} revealed that for mild reactions the rate per 1000 injections was practically identical for old arsphenamine and neoarsphenamine, somewhat lower for silver arsphenamine, sulfarsphenamine and Bismarsen (bismuth arsphenamine sulfonate). The incidence of severe reaction following sulfarsphenamine was 3.5 per 1000—a higher rate than that for arsphenamine or neoarsphenamine, due to the disproportionately high incidence of crustaceous dermatitis and purpura hæmorrhagica. Severe reactions from old arsphenamine (606) were no higher than from neoarsphenamine. The complexity and confusion inseparable from the reaction problem is well illustrated by the contrasting experience with sulfarsphenamine (used from 1925 to 1939) of the United States Naval Medical Department.^{152a} Among 29,438 injections reported, there were in the Navy's experience only 17 mild, 8 severe, and no fatal reactions to sulfarsphenamine. During the year 1939, 943 doses of this drug were administered with no reactions whatsoever. In the 15-year period the incidence of reactions to 1178 doses of sulfarsphenamine is somewhat higher than the average ratio of 1 to 1470 doses computed for 8 arsenicals, trivalent and pentavalent, used by the United States Navy. On the other hand, E. T. Burke, in his study of blood dyscrasias,¹⁸ maintained that although all sulfarsphenamines are much more prone to give rise to dermatitis and blood dyscrasias than are arsphenamine, neoarsphenamine or arsphenamine diglucoside, certain brands of sulfarsphenamine are much more likely to cause this particular reaction. He believed that the variation in the toxic effects observed in the use of different brands appears to be related to molecular structure and this, in turn, to process of manufacture. He appealed for a greater degree of standardization in this reported group of remedial agents. Just as the different arsenicals or brands of arsenicals, or even of lots of the same arsenical, vary in therapeutic potency, so may they vary in reaction-producing tendency. Sulzberger and Simon¹⁶⁶ noted in connection with the differing qualities of various lots and brands of neoarsphenamine that there was a varying sensitizing proclivity in man as well as in animals, for the various drugs. Cole and his associates,³⁹ in discussing the comparative number of complications among patients treated with arsphenamine and those treated with neoarsphenamine, found little or no difference in the number of reactions as between the two drugs (15% reaction for arsphenamine and 16.7% for neoarsphenamine).

Mapharsen (arsenoxide), it will be recalled, has as one of its strongest appeals and recommendations an exceptionally low incidence of reaction. Epstein,^{44d} compiling data from 92,000 Mapharsen injections from his own experience and the literature, found skin reactions, including exfoliative dermatitis, from one-half to one-third or even only one-ninth as frequent as with the other arsenicals. This was especially true of exfoliative dermatitis.

In common with Appel,²⁵ Jordon and Traenkle,⁷⁷ Cole and Palmer,²² Astrachan and Wise,⁷ Epstein^{44d} therefore recommends the use of Mapharsen in patients intolerant to other arsenicals. He suggests, in view of the experience of Parsons,¹¹⁸ Foerster and his associates,^{43,142} Kulchar and Barnett,⁴⁴ and Marshall,²³ all of whom reported recurrences of crustaceous dermatitis after the intravenous injection of Mapharsen or a pruritus and erythema after such an event, that patch

tests be used before the administration of Mapharsen to previously dermatitic patients. Fatalities^{81, 123, 126, 143, 145} to Mapharsen are extremely rare. Mention has already been made of the lessened toxicity of the Mapharsen when used in the continuous intravenous drip method of massive arsenotherapy as compared with neoarsphenamine. On the basis of lessened toxicity, Rein and Wise¹²⁶ have found arsenoxide (Mapharsen) a convenient medication for treatment of syphilis in office practice. In addition Mapharsen has been advocated, contrary to our considered opinion unless under expert direction, as a substitution product for neoarsphenamine and other arsenical drugs in various of the severe reactions. Acetyl-glycarsenobenzene (Solu-salvarsan)^{61, 64a} has been mentioned previously along with Thio-Arsene^{11, 32, 40, 129} as drugs which have been abandoned in this country because of high incidence of reaction. Trisodarsen's^{164a} reaction incidence is under investigation, though Givan and Villa,⁵² employing this drug in congenital syphilis, reported it well tolerated by intravenous and intramuscular routes. Bismarsen (bismuth arsphenamine sulfonate)^{60a, 111, 159, 167, 171} has a low incidence of reaction and in selected cases can be used as a substitute for other arsenicals to which the patient is reactive. The incidence of hematopoietic accidents is low, though a few recent cases have been reported. Sulfarsphenamine, silver arsphenamine, neoarsphenamine and arsphenamine have been adequately discussed in Part I of this review.

Diet, Nutritional State as Factors Influencing the Occurrence of Arsenical Reaction. In the past decade, and especially in the past 6 years, much progress both clinically and experimentally has been made on the effect of diet and other nutritional states on the background of arsenical reaction. There have, of course, been impressions that starvation, impaired nutritional states induced by the blockade in the First World War, poverty and other factors predisposed patients to treatment reactions from the arsenicals. It is now clear, however, from studies beginning with that of Craven,³⁵ substantiated by Schiffrin,¹³⁸ and recently further confirmed by Messinger and Hawkins,¹⁰² that for the liver at least, diet plays a major rôle in the prevention of damage by the arsphenamines. Craven³⁵ showed that dogs on a high fat and high nitrogen diet obtained maximum protection against liver injury resulting from the administration of arsphenamine. Of these two diets, Craven found that the former was more advantageous. A high carbohydrate diet, on the other hand, led to maximum susceptibility to liver injury caused by arsphenamine. He also indicated that starvation is an important factor predisposing toward liver injury caused by the arsphenamines. Cystine added to the diet or given intravenously did not increase the protective action of a carbohydrate diet. Schiffrin¹³⁸ came to much the same conclusion as Craven, with reference to the failure of carbohydrate diets to protect the liver against injury from arsphenamine, even when a large amount of glycogen was demonstrable in the liver. He found, however, in contrast to Craven, that a high fat diet also left the liver sensitive to the ill-effects of arsphenamine; but that a diet rich in albumin was the most effective in preventing liver injury by this agent. Beerman,¹³⁹ using rats instead of dogs, could not confirm or disprove the contentions of either Schiffrin or Craven. In 1940, Messinger and Hawkins¹⁰² found protein to be

most effective in protecting dogs against arsphenamine liver injury. On a protein diet the liver injury was trivial and promptly repaired. They, however, found a carbohydrate diet also beneficial but not as uniformly protective, and liver injury following this latter diet, when it occurred, seemed more severe. Fat proved to be deleterious and the fat-fed arsphenamine-treated dogs showed markedly progressive jaundice, severe liver injury and intoxication to the point of death.

Sulzberger, working with Mayer,¹⁶⁴ Simon¹⁶⁶ and others, on experiments with arsphenamine sensitization in guinea-pigs, found that guinea-pigs could be sensitized by intradermal injections of neoarsphenamine with great ease and regularity in Breslau, Germany; Boston, Mass.; Zurich, Switzerland; Odessa, Russia; and Ottawa, Ontario. But with the same technique, when fed on New York fodder, it was practically impossible to sensitize New York guinea-pigs in New York City. Sulzberger and Simon believed the cause of this variation in susceptibility to sensitization was not racial or constitutional, for New York guinea-pigs when transported to Breslau and Zurich could there be sensitized with ease. Sulzberger and Mayer believed that green fodder (alkaline ash) inhibited and dry fodder favored sensitization. Further observations reported by Sulzberger and Simon suggested that different lots of neoarsphenamine may have been factors in varying sensitizing effects as measured by a so-called sensitization index in men as well as in animals. They believe that this index is independent of the actual toxicity of the arsenical as such.

In the past 7 years beginning with the experimental work of Sulzberger and Oser,¹⁶⁵ there has been much interest in the question of relationship of vitamin C (cevitamic acid) to various types of sensitivity. The problem has been studied by a number of workers in connection with arsenic sensitivity in animals and in man. Certain of these investigators found that vitamin C, administered by various routes,^{14,24d,31,37a,b,39b,47,56,101,127,162,165,174,176} helped to prevent reaction to arsenicals while certain others^{25,27,42,50,94,178} have not been so convinced of the value of this vitamin as a reaction inhibitor. Darel^{19b} furthermore believed that using vitamin C in solvents for arsenicals reduced the therapeutic effectiveness of the drugs. This was denied by Dainow⁴⁷ and partially by Cornia.^{34a} This subject is in such a state of flux that it is impossible at the moment to say definitely whether vitamin C, administered orally or by parenteral route, has any significance in the reduction of arsphenamine reactivity. On the other hand, there is accumulating evidence to suggest that such a relation does exist, insofar as the use of vitamin C-containing solvents for neoarsphenamine administration has proven effective in reducing neoarsphenamine toxicity. Furthermore, Cornia^{34a} presented convincing evidence of the influence of vitamin C in arsphenamine sensitiveness, by giving 6 patients who had recovered from definite arsphenamine dermatitis, massive doses of vitamin C (500 mg. intravenously daily for 7 days). After a cautious intravenous test with minute doses of the same brand of arsenical which had produced the cutaneous reaction, 5 of the 6 patients were eventually able to take full doses of the arsphenamine without further cutaneous reaction. The patch test previously positive, became negative in 3 of 4 patients subsequently tested. Cornia kept

his patients' vitamin C levels high by daily oral administration of 100 to 200 mg. of the vitamin.

Wien¹⁸³ also made a study with large numbers of mice, to see the effects of simple variations in an ordinary laboratory diet on resistance of mice to mercurochrome and neoarsphenamine. His results confirmed the belief that in mice, the toxicity of the drug is among other things dependent on diet. He was able to demonstrate, for example, that in toxicity determinations of neoarsphenamine preparations made on various diets, different values were obtained for the average lethal dose under different diets. He suggested that toxicity determinations for arsphenamine preparations be made simultaneously with the standard brands.

Nervous States and Reaction to Arsenical Therapy. The influence of nervous factors on any of the arsphenamine reactions is difficult to evaluate. Suggestion, apprehension, and undue emphasis on the likelihood of reaction on the part of the treatment-room technician or physician at times seem to increase the occurrence of the immediate reaction. The mechanism for the production of such effects at least for cutaneous reaction has been discussed elsewhere.^{154,158} In addition, the repetition of visits to the clinic or office with the concomitant repetition of the same emotions which the patient experienced at the time of the first visit, when the diagnosis of syphilis was made, may lead to a heightened emotional state on the part of the patient. Eventually, prolonged therapy may lead to what Cormia³⁴⁰ has called the over-treatment syndrome, in which the patient complains of a striking degree of nervous irritability. Occasionally patients with this syndrome produced during arsphenamine treatment developed actual arsenical reactions, such as herpes zoster, nitritoid crises, and thrombocytopenic purpura.

Seasonal Influences on Arsenical Reactivity. Mention has already been made of Sulzberger's, Mayer's and their associates' work on the effect of differing geographic areas as factors in the sensitization proclivities of various arsenical drugs. This work, to some extent, is corroborated from the standpoint of the effect of seasons by the studies of Akiyama and his associates¹ who found among the reactions occurring in 3016 cases treated with arsphenamine in the period from 1921 to 1937, that the arsphenamine exanthemata were seen most frequently in January and June.

The Coöperative Clinical Group^{31a} made observations of the effect of different years in which the treatment was given on the incidence of treatment reactions to the arsenicals. The rate per 1000 injections for severe reactions dropped in all the clinics progressively from 1920 to 1931 inclusive. On the other hand, with mild reaction, after a great increase in the year 1921, the rate ran about level until the period 1926-29 when there was a pronounced increase which later dropped to the lowest level of the entire period. This increase in this 5-year period seemed to be explained as due to greater care in observing and recording mild reactions. Perhaps because of increased attention to mild reactions, the rate of severe reaction fell to a level of only 1.6 per 1000 injections in the years 1929-31 as against 3.1 in the years 1920-22.

From 1925 to 1933, in a comparison of the yearly incidence of post-arsphenamine and infectious jaundice, Wile and Sams¹⁸⁴ noted that

nearly 60% of their cases of late postarsphenamine jaundice occurred during the years 1930, 1931 and 1932. At the same time about half of the cases of infectious jaundice treated in the hospital from 1925 to 1933 occurred. Ruge¹³¹ and Stokes, Ruedemann and Lemon¹⁶⁰ had previously noted a close parallelism between the occurrence of postarsphenamine jaundice and infectious jaundice. In connection with seasons, the incidence of intercurrent infection at various times of the year probably plays a part in the frequency of reactions and in their severity when they occur.

Wile and Sams¹⁸⁴ in their study of jaundice in syphilis found that there was a tendency for late jaundice to be slightly more common in the winter months, but this is not so marked as with infectious jaundice. This tendency has been previously noted by others (Todd,¹⁷² Stokes, Ruedemann and Lemon,¹⁶⁰ Ruge¹³¹). Stokes, Ruedemann and Lemon definitely showed that their cases of jaundice were greatest in number during the months of respiratory and systemic infections, and approximately half the number had associated upper respiratory tract disturbances in the prodromal stage.

Pregnancy and Toxemia of Pregnancy in Treatment Reaction. The normal effect of pregnancy on the various organs of elimination would lead one to suspect that any other extraneous influence with potential hepatotoxic and nephrotoxic action would increase greatly the likelihood of reaction to the arsenicals in pregnant women. Furthermore, the question of whether arsenicals given to pregnant women could possibly increase the likelihood of the so-called toxemia of pregnancy needs fuller investigation. Several recent discussions of the subject, particularly that of the Coöperative Clinical Group,³¹⁶ by McCord,⁹³ and by Cole,²⁸ convey the impression that pregnant syphilitic women tolerate arsenical therapy well. McCord has apparently never seen a serious treatment reaction or death in the medical supervision of more than 2000 syphilitic pregnant women. On the other hand, Ingraham,⁷² in a carefully documented study of the complications due to arsenical therapy in syphilitic pregnant women, recorded 7 maternal deaths, the study being based largely on data obtained from antisyphilitic therapy reported from six different sources to the Committee on Maternal Welfare of the Philadelphia County Medical Society, since 1931. He was able in addition to collect 35 more deaths from the literature which he believes indicate that the pregnant syphilitic woman is not exempt from any of the severer types of treatment reaction, such as hemorrhagic encephalitis, acute circulatory collapse, damage to liver, arsphenamine dermatitis and aplastic anemia, all of which have been causes of death. He believes, moreover, that there is evidence to indicate that antisyphilitic treatment may aggravate an already existing toxemia of pregnancy, or precipitate an incipient one. Moore¹⁰⁵ has taken exception to Ingraham's findings and in a study sponsored by Moore and made by Peckham,¹¹⁹ it was shown that in a series of 13,742 consecutive deliveries at the Johns Hopkins Hospital, the incidence of toxemia of pregnancy was somewhat lower in syphilitic than in non-syphilitic patients. No correlation could be established in the study between the stage of syphilis at the time of its diagnosis and treatment during pregnancy and the frequency of toxemia. Peckham concludes that antisyphilitic treatment admin-

istered to syphilitic women during pregnancy does not increase the incidence of toxemia of pregnancy. The question of the influence of pregnancy on treatment reaction is still open, but the Reviewers feel that conservative individualized therapy during pregnancy with careful attention to detail will yield little or no excess of untoward reaction, in spite of the fact that individual isolated cases of serious reaction may occur in spite of careful control.

Rôle of Intercurrent Infection in Untoward Reaction to the Arsenicals. While this subject has been best worked out in connection with cutaneous reaction, undoubtedly the principles can be extended to apply to other types of reaction occurring in patients receiving arsenicals who are subject to intercurrent disease, fungus infection, or foci of infection. The rôle of intercurrent infection in untoward reactions to antisyphilitic treatment can be divided according to Dudley Smith¹⁴⁴ into two parts: 1, the harmful effect of antisyphilitic drugs on other infections; and, 2, the part which intercurrent infections play in producing harmful reactions in syphilitic persons. In 1921 Moore and Keidel¹⁴⁶ published an extensive study relative to the appearance of various skin diseases, including exfoliative dermatitis and other less complex reactions such as urticaria, erythema, herpes simplex and so forth following antisyphilitic treatment with arsenicals. They intimated that the secondary dermatoses like herpes could possibly result from something more than the actual local toxic effects of the arsenic, and were inclined to accept Milian's contention¹⁰³ that certain eruptions produced by the arsenicals are like acute exanthemata such as measles, and due to a lighting up of latent bacterial infection. Stokes and Cathcart¹⁵⁶ were pioneers in calling attention to the influence of focal and intercurrent infections on arsenical dermatitis. In 1934 Stokes and Kulchar¹⁵⁷ extended the concept to include dermatophytosis. According to these authors a part of the influence of infection was probably exerted through the allergic mechanism of arsphenamine sensitization, and involved the conception of multiple balanced and summation effects as suggested by Vaughan¹⁷⁶ in general, by Harkavy and Hebal⁶³ for infectious asthma and arthritis, and by the observations of Moore, Woo and Robinson¹⁰⁷ on the reactivity of atopics to arsphenamine intradermally. When the infection involves the skin in antecedent or induced dermatitis from other causes, the local dermatitic focus acts as an excitant to the general flare-up following arsenical medication. Dermatophytic infection may apparently act as a participant in a balanced or a "summation" allergic complex involving an arsenical, an arsenical extending the range and increasing the severity of the allergic dermatitic response to the drug. A dermatophytic focus may also conceivably serve through the induction of local vasodilatation as the starting point of an "arsenical" dermatitis. Minute amounts of arsphenamine in arsphenamine-sensitive patients may flare up and generalize a local, apparently mycotic, dermatitis. The interaction of a drug on infection allergy may be reversible, and may in some cases take the course of Milian's "activation" of the infectious focus with the appearance of an exanthem of the toxic erythema type and a flare-up of the local focus in the case of bacterial infection, or an exacerbation of a localized mycotic process or a "mycotid" in the case of a fungus infection. Their experience led Stokes and Kulchar¹⁵⁷ to suggest that in dealing with an arsphenamine

mine dermatitis in patients with focal infective lesions, mycotic or bacterial, treatment should be directed, albeit with caution, at the focal as well as at the general process. In 1937 Stokes and Callaway¹⁵⁵ expressed the opinion that intercurrent infections like influenza may exercise a sensitizing influence to pyogenic and mycotic dermatoses as well as to light. Smith, in his study, quotes a number of observers, one of whom, Weiss¹⁸¹ pointed out in 1925 that fatal accidents following antisiphilitic treatment sometimes can be prevented if caution is observed in treating patients with acute infections, especially pneumonia. The pneumonia induction may be in part due to mechanical and allergic effects involving the pulmonary circulation. He also cited Cormia^{34a} (1936) in his work on experimental arsphenamine dermatitis which showed that staphylococcus toxin did not increase the incidence or severity of the reactions to arsphenamine in guinea-pigs, and similar results were observed in guinea-pigs infected with streptococci. Smith comments that this does not reproduce the situation found in intercurrent infections in man. Netter and Urbain¹¹⁰ felt that from their studies with the virus of herpes zoster that arsphenamine as well as other agents is responsible for cases of secondary zoster because the drug possibly stirs up to activity a latent virus in the ganglia. Much of the jaundice which occurs during arsenical therapy and is attributed to the tonic effects of the drug is in all probability the expression of an epidemic of infectious hepatitis. (Stokes, Ruedemann and Lemon,¹⁶⁰ Ruge,¹³¹ Wile and Sams,¹⁸⁴ Lane⁸⁷ and others.)

Technical Elements in Reaction Production. It is not intended under this heading to discuss such well-known causes of reaction as the use of deteriorated drugs, aëration of neoarsphenamine through shaking, improper alkalization of arsphenamine and so forth.

In 1931 Hirshfeld, Hyman and Wanger⁶⁵ produced and described "speed shock." They demonstrated that the rapid intravenous introduction of pharmacologically active or inert chemicals, drugs and biologic fluids may frequently give rise to immediate and far-reaching non-specific sequelæ, at times serious and occasionally fatal. The clinical syndrome of "speed shock" occurs 40 to 60 seconds after injection. The reaction was apparently not a species idiosyncrasy since it could be obtained in cats, dogs, monkeys and man. Anesthetics and narcotics were unimportant factors in production since the syndrome was produced in unanesthetized animals. The antidote to speed shock was a slow infusion or intravenous "drip," which was developed for various purposes and lately introduced into chemotherapy. Hyman and his colleagues^{65, 69a, b, 70} felt that if the concept of "speed shock" were correct and the immediate toxic effect that followed the introduction of chemotherapeutic agents were technical rather than pharmacologic, potent therapeutic agents might be administered in "doses far greater than at present employed, and this without serious damage to the cells of the host." This concept has reached fruition in the intravenous arsphenotherapy. Hyman, in an interesting study on the subject,⁶⁵ compared the toxic phenomenon of the intravenous massive dose chemotherapy with routine treatment. Contrary to expectations he states that there do not appear to be late toxic complications arising from excessive dosage or accumulation, although difficulties due to idiosyncrasies do crop up unexpectedly causing treatment morbidity

and treatment mortality. The incidence of these closely approximates those of routine therapy and because the results of therapy approach the goal of the chemotherapist, Hyman believes they would seem to justify the hazards of increased toxicity if present.

The incidence of reaction in massive arsenotherapy has been well studied by the Baehr-Chargin group.¹⁰ In his recent compilation of the toxic manifestations, Chargin illustrates the complexity of this problem of dosage and reaction incidence. He states that in previous experience with 111 patients treated by the continuous intravenous drip method with neoarsphenamine, there was 1 fatality due to hemorrhagic encephalitis and 1 recovered case, and a rather high incidence of polyneuritis (38%). This led to the substitution of Mapharsen for neoarsphenamine, which subsequently proved to be less toxic and possibly equally efficacious therapeutically. This substitution of one drug for another is not as simple an explanation as it would seem on the surface, for the cause of the difference in toxicologic manifestations, inasmuch as the Mapharsen was used in a dosage much lower than that previously employed in the case of neoarsphenamine (1200 mg. Mapharsen as compared with an average dose of 4 gm. (4000 mg.) neoarsphenamine). From the experimental side, however, Magnuson and Raulston⁹⁸ found that the maximum tolerated dose and the minimal lethal dose are such as to indicate the need for considerable caution in the administration of massive doses of Mapharsen to patients by the continuous drip method.

In a preliminary report on the rapid intensive treatment of early syphilis with multiple injections of Mapharsen, comprising 275 cases treated with Mapharsen alone and 141 cases treated with Mapharsen and fever, Thomas and Wexler¹⁶⁹ showed that the combination of intravenous typhoid vaccine and Mapharsen, especially when both are administered the same day, give more frequent transitory toxic effects than Mapharsen alone, but no clinical evidence of hemorrhagic encephalitis developed in 141 cases. By reducing the number of fever bouts and omitting Mapharsen the days when fever is given they believe the occurrence of even minor toxic effects can be materially reduced. Cannon²²⁶ using a simplified syringe technique for administering old arsphenamine (606) gave 16,943 injections to 1187 patients (1053 adults and 134 children); 77% of these injections were well tolerated.

Another technical consideration which has recently been pointed out in connection with new drugs but for which there is no apparent explanation, is the rate of injection by the syringe method of neoarsphenamine as compared with Mapharsen. The former must be injected slowly in order to avoid reactions, whereas Mapharsen is better tolerated when injected by rapid procedure.

Consideration of Individual Types of Reactions to the Arsenicals:
Cutaneous Reactions. New types of cutaneous manifestations have been recently reported which deserve only mention, as follows: vesicobullous dermatitis,¹⁰⁸ unusual reticular fibro-atrophoderma,^{41c} and vitiligo.²³ Fixed eruptions due to the arsphenamines have been thoroughly reviewed by Chargin and Leifer²⁶ whose series (69 patients) seems to be the largest recorded. Of these 69 receiving one of the trivalent arsenicals, the drug was clearly responsible for the fixed eruption in 68. Chargin and Leifer felt that race was an important pre-

disposing factor inasmuch as 79% occurred in negroes, 19% in whites, and 2% in the yellow races. The lesions were most common on the face and were also observed over the entire body, but not on the scalp, palms and soles. The mucous membrane of the mouth was involved in 2 cases. In descending order of frequency the precipitating drugs were arsphenamine, neoarsphenamine, silver arsphenamine, Mapharsen, and Trisodarsen. Lesions produced by one trivalent drug may be activated by other trivalent drugs and also by some pentavalent drugs. Activation only follows the use of the intravenous or intramuscular route. Patch tests and iontophoresis have been consistently negative. Full-thickness autotransplants of the involved skin in 3 patients failed to react when the drug was readministered. None of these cases progressed to exfoliative dermatitis or any other type of arsenical dermatitis in spite of continued arsenical therapy. Since all trivalent arsenicals do not produce fixed eruptions with equal frequency, it is possible to continue therapy uneventfully by changing the type of arsenical.

While according to the work of Osborne and his co-workers^{114a, b, 115} (*cf.*¹⁶⁸) the trivalent arsenicals and the pentavalent arsenicals have a different point of attack in the skin, reports have now appeared which would tend to indicate that the possibility of sensitization to both trivalent and pentavalent arsenicals in the same patient is possible. This concept was exemplified by the cases of Epstein,^{41b} Golz⁵⁸ and Franks and Fisher.⁴⁹ This observation should lead to caution in further arsenical therapy with a pentavalent compound in a patient who has once recovered from a reaction to a trivalent arsenical compound.

Another cutaneous reaction to arsenical therapy worthy of mention is the so-called erythema of the ninth day. This cutaneous reaction has been redescribed by a number of individuals, including Keim,⁶⁰ Epstein and Levin,⁴¹ Goldman and his associates,^{56, 57} Sprafke,¹⁴⁸ Peters (*Am. J. Syph. Gonorr. and Ven. Dis.*, 25, 527, 194), and others.^{21, 66b} This eruption, originally designated by Milian as "erythema of the ninth day," is an entity which should be differentiated from the exfoliative dermatitis of arsenical causation and certain acute exanthems. The mechanism of this reaction is unknown. Milian considered it a toxic erythema from the flaring of a latent non-syphilitic infection focus by the drug. Other speculations include a supposed response of the autonomic nervous system to either the dose or the type of trivalent arsenical or the mode of injection. The eruption is usually acute, coming on 7 to 10 days after the institution of arsenical treatment, and thus usually with the second injection. The onset suggests that of an acute infection with chills and fever 24 hours after the injection. From about the second to the fourth day the eruption appears and may be indistinguishable from that of measles or even a rather coarse type of scarlatiniform erythema. Edema of the eyelids often occurs but there is usually no coryza. The comparatively small degree of involvement of the mucous membrane without Koplik's spots assists in differentiation. This process is self-limited and may or may not be associated with a variety of complaints. Further arsenical treatment is not contraindicated.

The newer conceptions of the clinical aspects of postarsphenamine dermatitis have been sufficiently described (Stokes,¹²³ Sulzberger,¹⁷¹ Cornia,⁷⁶ *et al.*, E. Epstein^{41a} and many others). Whether or not arsenical therapy can be continued after this complication is always a

critical question. Patch tests with the arsenical have proved unreliable (Beerman^{13d}) and the possibilities of the harmful effects from them have been pointed out by Bechet,¹² Beerman,^{13a} and Schoch.^{139a,b} Cautious testing of tolerance by intravenous testing of minute doses has been proposed by Robinson.¹²⁸ Schoch and his collaborators¹⁴⁰ side-step the difficulty by substituting Mapharsen successfully for the arsphenamine in 40 cases. The initial dose for the tolerance test should be 1 mg. Even minute doses are not tolerated by patients who have once sustained a severe exfoliative accident after neoarsphenamine. Schoch and his co-workers found that patch-testing with Mapharsen (3.3% solution) is a more reliable test of tolerance than the corresponding concentration of neoarsphenamine in patch-tests.

Liver Damage Due to Arsenical Compounds. The pharmacologically known hepatotoxicity of arsenic has led to a good deal of post-hoc thinking on the hepatic reactions to arsphenamine and other antisyphilitic arsenical treatment. When a patient under treatment with an arsenical develops jaundice, not less than six, and probably several more possibilities must be considered. It has become increasingly clear that epidemic waves of postarsenical jaundice, many cases occurring months and sometimes years after the exhibition of the drug, are in reality catarrhal infective accidents to which the drug may or may not have served as a predisposing cause (Stokes, Ruedemann and Lemon,¹⁶⁰ Wile and Sams,¹⁸⁴ Sager.¹³⁴ (See also ^{5,20,51,59,62,74,75,85,87,96,112,124,131,146,147,180}.) The entire subject has recently been thoroughly reviewed by Lane⁸⁷ on the basis of a series of 100 of his own cases, from which he concludes that syphilis alone seems a relatively rare causative factor; that arsenic alone does not explain the complication, though it exerts an influence in most cases; that bismuth appears to participate in some degree; that tryparsamide can produce jaundice as well as the trivalent arsenicals, and that death may occur late from hepatic cirrhosis. The discussion of this paper supported in general the conception that antisyphilitic treatment is a contributing but not a sole factor in the induction of hepatic injury. Soffer^{146,147} detected racial differences (whites three times as frequently jaundice as negroes), but no influence from the stage of the syphilitic infection or the stage of treatment. Gott and Doyle⁵⁹ confirmed the racial difference, and found that Mapharsen produces jaundice 10% less frequently than neoarsphenamine. The possibility of minute amounts of arsenic in preparations credited with the production of jaundice has been investigated by Russell,¹³³ and Lowenburg and Naide⁹¹ with negative results.

Hemorrhagic Encephalitis. Various named pericapillary encephalorrhagia (Globus and Ginsburg⁸⁴), brain purpura (Alpers²), and arsphenamine encephalopathy (Levy⁸⁸), this occurs "normally" once in every 5398 treated cases, or 1 case in every 28,758 injections of an arsenical (Glaser, Imerman and Imerman⁵³). The occurrence of the reaction like a bolt from the blue, virtually without warning, and accompanied by an exceedingly high mortality, make it one of the most disturbing complications of treatment for syphilis. Glaser and the Imermans point out that the reaction occurs in non-syphilitic persons, apparently without relation to age or sex, or to the dosage of the drug administered, to the number of injections given, or to the intrinsic toxicity of the preparation. The reaction occurs most commonly after

the second dose; may develop within 12 hours or after a latent period as long as several days. It was formerly almost invariably fatal. The prognosis has, however, steadily improved in recent years through the use of repeated lumbar puncture, sedation, adrenalin, and especially dehydration, including intravenous hypertonic solution. A prodrome of confusion with conduct abnormalities may permit the recognition of an incipient case before a second injection is given, and a fatality be thus avoided. The autopsy picture in the brain is that of dilatation and engorgement of meningeal and cerebral vessels with a picture suggesting "wet brain," plus vascular necrosis and perivascular hemorrhage of the "ringed type." (See ^{16,34,53,116,117,130,132,173a,b}.)

Hemolytopoietic Reaction to Arsenicals. Enough interest has been aroused by hematopoietic damage attributed to arsenicals in the treatment of syphilis to provide the basis for a separate review. (See ^{9,15,17,36,44,45,46,66,67,71,78,79,81,89,90,92,101,135,137,161,170,185,186}). Burke's views have been alluded to. Every drug now in use in the treatment of syphilis, including Mapharsen, has been shown to be capable of producing hemolytopoietic reaction, so that the substitution of one drug for another, as suggested by Falconer and Epstein and their group^{42,44,45} as well as Goldberg⁵⁵ is certainly not free from risk. Epstein and Falconer⁴² in studying 8 patients who had had a thrombocytopenic purpura following neoarsphenamine or Bismarsen, were able to show that very minute amounts of the offending drug or a related member of the group, was capable of reviving the thrombocytopenic reaction, and that successive reactions led to increasing sensitiveness to the drug, so that repetition of treatment after evidence of thrombocytopenia had once developed, is definitely and indeed exceedingly dangerous. Vitamin C was employed in large doses and in the diet in an attempt to control the thrombocytopenic reaction, without effect. Subthreshold hemolytopoietic reaction was clearly recognized in 30 patients who, although they tolerated antisypilitic treatment without clinical reaction, sustained diminution of leukocytes and platelets in the peripheral blood following each treatment. Mapharsen appeared less likely to produce these changes than neoarsphenamine. The simultaneous use of two drugs known to influence the hemolytopoietic system is a matter for concern in patients simultaneously treated for syphilis and gonorrhea with an arsenical and a sulfonamide. Caletti¹⁹ observed no ill-effects from such synchronous use of drugs with known hemato-poietic effect, and concludes that intolerance is a matter of the individual drug, and not of synergistic use.

New Methods of Reaction Prevention. Doak,³⁵ Appel^{3a} and Jankelson⁴ and also Shaw¹⁴² have contributed important studies. Doak in particular reviewed the use of sugar, calcium salts, degradation products of protein including the aminoacids and other substances and compounds recommended for admixture with the arsphenamine solution, before administration.^{39c,52,97,125,141,177} The question of the efficacy of these substances remains open. The possible influence of vitamin C previously mentioned is supported and opposed by about equal numbers of observers. MacKee and Astrachan^{6,23} who over a period of years have employed liver extract as a detoxifying agent in intolerance to arsenicals, heavy metal and irradiation, have felt increasingly certain that liver extract is a valuable detoxifying aid. Sodium thio-sulfate has been

the subject of a number of studies and publications by Ceder, Zon, and Klinger,²⁴ Ayres and Anderson,⁸ Muir, Stenhouse and Becker,¹⁰⁹ Oppenheim and Fantl,¹¹³ and Mattice and Weisman.¹⁰⁰ Ceder and his associates²⁴ conclude that while there is still room for controversy, much of the disparity of opinion is due to artefacts and technical difficulty incident on arsenical analysis and on the selection of subjects. In a study of 10 patients under treatment with an arsphenamine and in whom urinary, fecal and total arsenic excretion was carefully studied, the 6 receiving sodium thiosulfate exhibited no significant differences from the 4 who did not receive sodium thiosulfate. It is concluded therefore that this drug, whose reputation has supposedly rested on its ability to facilitate the elimination of arsenic, if effectual at all, is certainly not so because of any influence on arsenic elimination. Clinical syphilologists have in general discarded sodium thiosulfate in the treatment of arsenical reactions.

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Correction. In Dr. Sodeman's review of "Chronic Constrictive Pericarditis" in the July number of this journal (page 133), in the sentence reading "Dyspnea may occur on exertion, but in the absence of pleural fluid, orthopnea is present," the word "present" should be changed to "absent," so that the sentence will read that "orthopnea is absent."

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ORIGINAL ARTICLES.

**SOME MEDICAL, SOCIAL AND ECONOMIC PROBLEMS OF THE
PHYSICALLY HANDICAPPED.***

BY ALFRED RIVES SHANDS, JR., M.D.,
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THE medical, social and economic problems of the physically handicapped are linked together so closely that in a short discussion it is difficult to separate these into three distinct subjects. Your speaker, being an orthopedic surgeon, now limiting his clinical work entirely to children, cannot help but focus attention to this younger group. Approximately 80% of the crippled children present physical handicaps carried through into adult life, so that almost any discussion of the child will also be applicable to the adult.

In referring to the child as a problem of the physically handicapped, it is apropos to quote from the "Crippled Child's Bill of Rights" as adopted several years ago by one of the national societies for crippled children: "Every crippled child has the right to the best body which modern science can help it secure; the best mind which modern education can give; the best position in life which his physical condition perfected as best it may be will permit; . . ."

First the best body! What are some of the more common conditions causing a crippled body, and what are some of the things to be done to make this a better body? Infantile paralysis, as a cause for crippling in childhood, has for years held first place. More and more investigative work, however, is being done—especially that sponsored by the National Foundation for Infantile Paralysis—and it may be that the means of prevention is now close at hand. The methods for the care of the paralyzed muscles are being constantly improved, most of the deformities can be corrected, the unstable joints can be made stable, and often braces can be applied

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to allow weakened and paralyzed parts to be used which would not function otherwise. Congenital club feet and congenital dislocation of hips constitute two other major causes for crippling in childhood. If these two conditions are treated early, often the recovery will be such that it is difficult to tell there has been a physical handicap. If they are treated later in life, nearly always an improvement can be expected. The infections of bones and joints caused by the tubercle bacillus or the streptococcus or staphylococcus are responsible for a large number of the physically handicapped. With the miracles of chemotherapy, resulting from the use of sulfanilamide and its derivatives, and with the use of antitoxins, the severe infections from the streptococcus and staphylococcus are being less feared and becoming less numerous. The incidence of tuberculosis of bones and joints is less, due to the campaigns to control the milk supply and the contact of those known to have pulmonary tuberculosis with healthy ones. About 50 years ago, one-half of all the crippled children were crippled because of tuberculosis; now the incidence is 5% or less. The developmental deformities of legs, such as bowlegs and knock knees, due to rickets and other nutritional disturbances, now are fewer and fewer, due to the improvement in infant care and the appreciation of certain vitamin-containing foods. The two crippling conditions with which little progress has been made in either the prevention or the treatment of, are spastic paralysis and progressive muscular dystrophy. Research is certainly needed to find out more about their causes. These are only a few of the more common conditions causing crippling in childhood.

Second, the best mind! How can this be obtained and what problems are presented? In nearly all large cities, there is now special provision made for special classes for the teaching of the crippled child. However, this does not in any way adequately meet the situation. There are about 100,000 crippled children in need of special education, and this is provided for only 25% of this number. The two principal reasons for this unfortunate situation is: 1, that the cost is from 3 to 5 times as great to educate a crippled child as a normal one; and, 2, that a large part of these crippled ones live in the rural areas where both the transportation to special classes in the schools, if there were such, and the cost of same would be difficult to arrange. Hence, the education of the crippled one in the rural areas has become one of the greatest of the needs in the care of crippled children. In planning the education of the crippled child, whether academic or vocational, the mental abilities of the child must be carefully studied, evaluated, and then developed. Perhaps there is a greater need for the so-called progressive education for the crippled child than for the normal one. Certainly his aptitudes for specific types of study and work should be given special attention, and emphasis placed upon these in his education. If he likes to write, and has imagination, let him think in terms of being an author and writer.

His physical disability should not in any way handicap him for this vocation.

And third, the best position in life! How is this to be obtained? This is dependent upon the handicapped one's social and economic adjustment. After all, a successful adjustment should be the ultimate goal for all programs of the physically handicapped. It is important for the handicapped one to have a good morale. This may vary with his power and ability to earn a living; hence he should be given every opportunity possible for physical and vocational rehabilitation. If he is successful in his economic adjustment, there usually follows a good social adjustment. He then will meet society on an equal level, and social relationships with normal ones will be normal without allowances being made for his handicaps. He will be competent in his employment, self-confident, independent, successful, and happy. If there is an unsatisfactory social and economic adjustment, he will become increasingly dependent upon society, and will undoubtedly become more lonely, isolated and unhappy. Everything possible should be done to avoid this condition.

In discussing the problem of the crippled one, a word should be said about sympathy. This should never be given! It is demoralizing to the person, and so often leads to unnecessary dependency. Self-reliance on the part of the crippled child or adult is to be desired, of course, and this cannot be obtained if friends and parents are constantly emphasizing the disabilities, saying how sorry they are for him, and offering a helping hand when he can take care of himself. Crippled ones should associate with the normal insofar as it is possible, and their handicaps completely overlooked. They should definitely not be segregated in their social and community life, although it may be necessary to have special classes for their education. They have crippled bodies, but not crippled minds. If too much sympathy and assistance is given, their minds will become crippled, they will be self-centered, self-pitying and definitely introspective. This attitude of mind, if allowed to develop, will be much more difficult to correct than the physical deformities and disabilities. Their social adjustment cannot be satisfactorily made; they are unhappy, and those responsible for them become unhappy.

A word particularly about the crippled adult. Before a physically handicapped adult is started on his path to independence and self-sufficiency, there must always be an accurate appreciation and evaluation of his medical, social, and economic status. A study should be made also of his special aptitudes, his intelligence, his temperament, and his interests. Perhaps this can best be understood by giving an example of a typical vocational rehabilitation problem. A carpenter falls from a high scaffold and suffers a broken back and two broken heels. He is in the hospital for months, but finally comes out on crutches, and with a back brace. He has always been a carpenter, knows no other occupation, but it is very evident he will never be

able to go back to carpentry. First, his physical condition shows weakness and deformity in his back and painful heels. He has been interested in mechanical things, and working with his hands all his life. He is of good intelligence, has an optimistic temperament, has always been conscientious and industrious, and does not want to remain idle in mind or body. Given a vocational training in something he can do while sitting, he will be able to earn his own living again. Watchmaking appeals to him; he learns fast and is trained in 6 months' time. There is a demand for good watchmakers. Twelve months later he is not only earning his own living, but is able again to be the sole support of his family. He is definitely back into the economic life of the community in a very remunerative and self-supporting job, and quite competent to make his own way. Through vocational rehabilitation, his economic problems have been solved, and a normal social readjustment will follow.

Several years ago, your speaker was deeply impressed with what the director of a large crippled children's vocational school in Denmark told him; namely, that the problem of the crippled one, whether adult or child, had three equally important parts: 1, Medical care; 2, Education and Training; and 3, Placement in work. He believed and emphasized the point that medical care should never be undertaken unless it was possible to carry on with the other two. Since hearing this statement, I have constantly and repeatedly thought that this should also be our perspective of the ultimate solution of our problem. Any comprehensive program for the care of the physically handicapped should include these three parts. If our national program included such, it could be said our program is adequate; but unfortunately it can be called adequate in only certain parts of our country. It is the ideal, but it is certainly not beyond our realization.

In conclusion, some remarks made by Dr. Robert B. Osgood of Boston relative to the crippled child, also applicable to the crippled adult, sums up most clearly what we are trying to accomplish for the physically handicapped one, and tells the story in the fewest words to those of you unfamiliar with our work with cripples; namely, "What we want to do is to get the crippled child back into the community, so trained that he can compete not as a handicapped person, but if you please, as a person who will have no fear and ask no favor; a person who will be able to earn his way both intellectually and materially with just as little allowance made for his particular handicap as possible. That is the star to which we shall hitch our wagon." This is indeed a bright star, but not one so high that it cannot be reached. It is not far above the heads of those handicapped ones who are presented with the facilities for medical care, education, training and placement in work. Our part as doctors and workers in the field is to create, and help to stimulate the creation of, these facilities. Through the state and private

agencies, and the helpful attitude of the general public and legislative bodies, the physically handicapped ones are now gradually everywhere being given a larger helping hand in their struggle to compete with the world for a normal social and economic life. Every state and community does not yet have a complete program of medical care, academic and vocational education, and placement in work for the physically handicapped, but many do, and the facilities each year are being improved in the others so that ultimately our national program undoubtedly will be called adequate, or as it has been so aptly expressed, "We may reach our level of aspiration," and then our ideal will be realized.

WERNER'S SYNDROME: REPORT OF THE FIRST NECROPSY AND OF FINDINGS IN A NEW CASE.*

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In 1934 we reported the first 2 American instances^{6a} of a condition which we re-named Werner's Syndrome.⁸ Since then we have had a necropsy of one of the patients and the opportunity of observing an additional case. This is a heredofamilial disorder^{6b} characterized by canities (*i. e.*, premature graying of the hair), premature baldness, sclero-poikiloderma, precocious cataracts, endocrine stigmatization and a characteristic physical habitus. The individuals are frequently short in stature, gracile in build, with some features of juvenilism which suggest retarded or arrested development, and others, such as the canities and vascular changes, which indicate a premature senescence. Hypogonadism occurs in both males and females. Two of our patients presented blue scleræ. Osteoporosis was present in the 3 cases. Metastatic calcification including calcification of the vessels was prominent. In the previous publication we could offer no satisfactory explanation of the etiology or of the pathogenesis of the bizarre syndrome. There seemed to be a pluriglandular disturbance; the preponderant involvement of ectodermal structure and the disturbance of calcium metabolism pointed chiefly to the participation of the parathyroid gland. Subsequent observations, both clinical and laboratory, have tended to confirm the original suspicion that it was the parathyroid among the ductless glands that was especially implicated.

The following case histories present the clinical and laboratory

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data on these 3 patients suffering from this syndrome; in the first 2 only the histories subsequent to the previous reports will be given including the report of the first necropsy on any case of Werner's syndrome. In addition, the history of a third patient still under observation is reported in full.



FIG. 1.—Case 1. Werner's syndrome.

CASE 1 (Fig. 1).—D. G. *Subsequent History.* Since the previous publication⁶ he has been continuously hospitalized. The out-standing feature

has been a progression of the scleroderma with ulcerations, infections and localized gangrene of the lower extremities (Fig. 2) to such an extent that amputation of the right leg below the knee joint had to be performed on May 10, 1938, and of the left leg on June 13, 1939. He has had repeated attacks of ulceration over the left olecranon process. Since February, 1937, he has suffered from recurrent attacks of keratitis which have resisted treatment. At the time of writing, the whole right cornea presents a steamed, opaque appearance. He has also suffered from recurrent attacks of trigeminal neuralgia. Since 1940 he has been presenting cardiovascular symptoms, *i. e.*, occasional precordial pain relieved by nitroglycerin, blowing systolic murmurs over the precordium, pulsus alternans, elevation of the blood pressure to 168/90, and electrocardiographic changes. Fundus examination showed narrowing and tortuosity of the vessels.

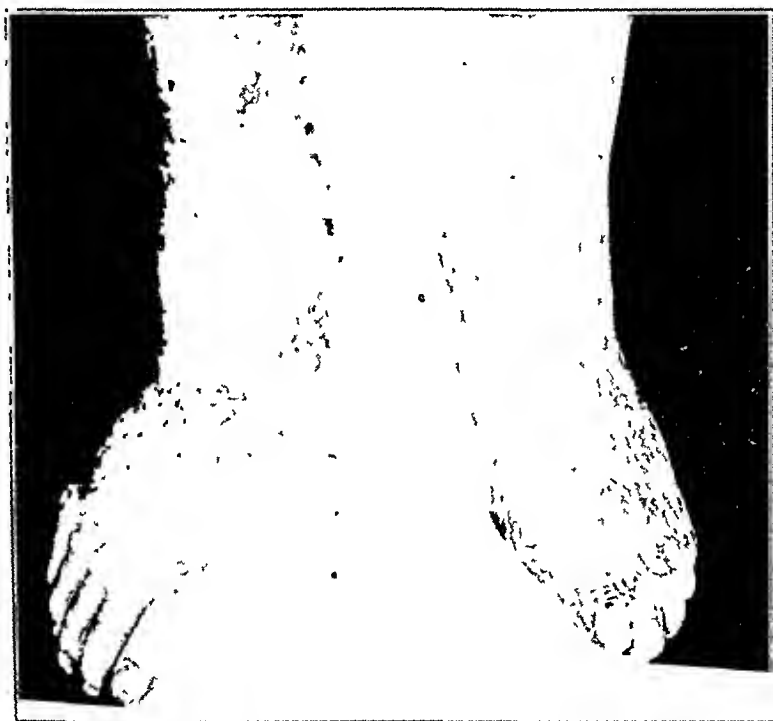


FIG. 2.—Case 1. Scleroderma and ulcers in Werner's syndrome.

Laboratory Data. The Hamilton test did not show any increased parathormone. The urine and blood counts have not changed materially since the previous report. Repeated glucose tolerance tests showed a flat curve. Blood calcium has ranged from 9.5 to 11.0 mg. per 100 cc., and phosphorus from 2.5 to 4.2 mg. per 100 cc. Phosphatase was 7 Bodansky units. The blood CO_2 combining power was 62.5 vol. %. The serum albumin was 4.4% and the serum globulin 2.6%.

Roentgen ray of the right wrist on September 19, 1938, showed extensive destruction of the lower articular surfaces of the radius and ulna. Several carpal bones in this region showed an irregularity in contour with evidence of a mottled decalcification. The vessels and the soft tissues showed very extensive calcific deposits. Teleoroentgenogram showed some cardiac enlargement, and calcific deposits in the arch of the aorta. The electrocardiogram showed flat *T* waves in Leads 1 and 2, and inversion of the *T* waves in Lead 3 (no digitalis).

CASE 2 (Fig. 3), A. G. *Subsequent history including necropsy report:* Since the previous note on this patient in 1934, he has had three admissions to Montefiore Hospital. The first was for recurrent ulcers and gangrenous cellulitis of the left foot (Fig. 4); at this admission the liver was found

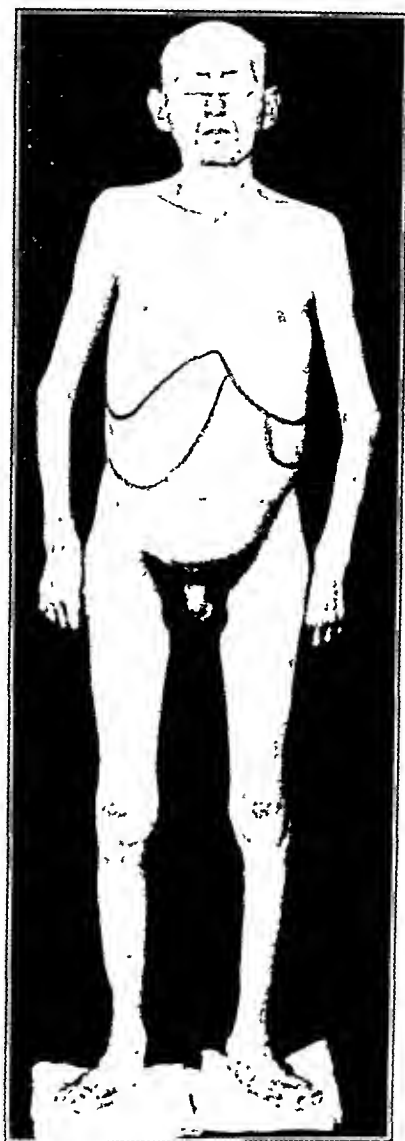


FIG. 3 — Case 2. Werner's syndrome.

enlarged to four fingers' breadth below the free costal margin. The second admission was for ulcerations and cellulitis of the right foot, and an amputation of the big toe and head of the first metatarsal bone had to be performed. The third and final admission on March 11, 1939, was for recurrent

ulcers of the right foot and progressive weakness. The latter was found to be due to an apparently primary tumor of the liver with ascites, secondary anemia and splenomegaly. In addition to the previous findings, peripheral



FIG. 4.—Case 2. Scleroderma and ulcers in Werner's syndrome.

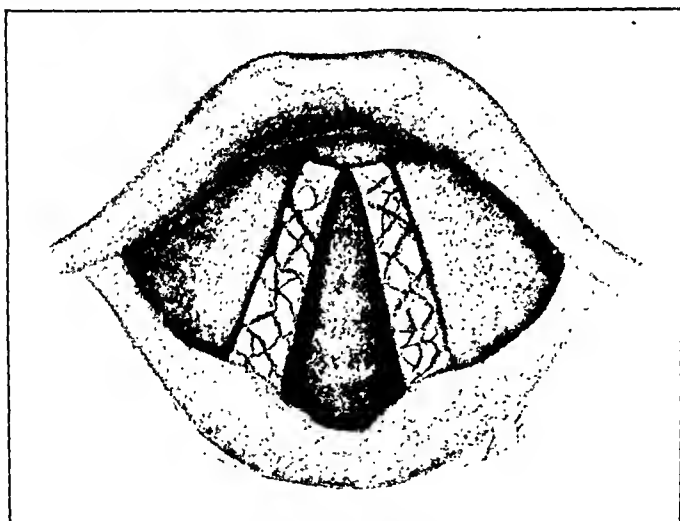


FIG. 5.—Case 2. Larynx.

pulsations could not be felt in the arteries distal to the axillary and femoral arteries, an enlargement of the heart appeared, limitation of the range of motion of the left elbow and both wrists were noted. The telangiectases over

both knees were more prominent, and appeared on the scrotum. The voice was high-pitched. Laryngoscopy performed by Dr. Rudolph Kramer presented a bizarre picture with dilated vessels on the vocal cords in the midst of a congested mucosa (Fig. 5).

Laboratory Data. The Hamilton test was positive for excess of circulatory parathormone (Baumann and Sprinson). The blood calcium was 11.9 mg. per 100 cc., 13.0, 11.1, 10.7, 12.7, 12.0 and 13.1. The blood phosphorus was 2.5 mg. per 100 cc., 3.7, 3.9, 3.0, 3.8, 2.7. The blood phosphatase was 4 and 8 Bodansky units. The blood urea was 14.8 mg. per 100 cc., 17.8, 12.3 with a pre-agonal rise to 22.7. The total blood protein was 6.9 mg. per 100 cc. (serum albumin, 3.0; globulin 3.9); uric acid, 3.5 mg. per 100 cc.; cholesterol, 244 mg. per cc. Blood count showed secondary anemia. Basal metabolic rate was -6% and -8% . The electrocardiogram showed left axis deviation and an abnormal A-V conduction time to 0.24 second.

Roentgen Ray Examination. Skull: sella turcica smaller than normal, but no destruction, slight hyperostosis of the frontal region. Abnormal calcification was found in the following locations: the large and small vessels of the arms and hands, a large plaque about the elbow, in the vessels of the entire lower extremities, in the soft tissues around the knees and feet, in the abdominal aorta and some of its branches, and in the pelvic arteries. This calcification afforded an exceptional visualization of the involved vessels. Productive arthritic changes were demonstrated by Roentgen ray in the bones of the hands, the feet and the dorsolumbar spine.

Death occurred from a terminal pneumonia on September 6, 1939.

Autopsy (14 hours postmortem by Dr. D. G. Freiman). The body is fairly well developed and well nourished; it appears much older than the given age. Scalp is bald except for a narrow gray tonsure. Skin of face is smooth, beard very light. Corneae are cloudy. There is a coloboma in the right eye and the pupil of the left eye is moderately contracted and slightly irregular. Gums are edentulous. There is no palpable adenopathy. Pubic hair is scanty. External genitalia are hypoplastic, penis and testes being very small. There is slight pitting edema over the lower legs and feet. Both feet show some scaling of the skin and there are several very shallow pink or yellowish-pink ulcers; one located over the left internal malleolus and several over the bony prominences on the soles of the feet. The right great toe has been amputated. The left 5th toe is missing. There is considerable hallux valgus. Telangiectases are present over both knees. Both patellae and in a few spots the upper end of the tibiae are somewhat roughened. The knees are prominent. There is a moderately heavy panniculus. Abdominal cavity contains about 2 liters of slightly blood-tinged fluid. Liver and spleen extend below the costal margin. Both pleural cavities contain about 1 liter of straw-colored fluid. Pleural surfaces are smooth and show no adhesions.

Larynx. Mucosa is pale. The true vocal cords, particularly the left, show areas of red discoloration which appear to be submucous hemorrhages. *Thyroid* (weight, 12 gm.) is quite small and firm, cuts with some resistance, revealing a reddish-pink parenchyma containing a little colloid. There are several small adenomas less than 1 cm. in diameter. *Parathyroids:* Only two found. These are slightly larger than average and one shows a few dark areas of discoloration.

Lungs. On section, the lungs are pink and slightly rubbery. From some areas a small amount of pale frothy fluid can be expressed. There are no areas of consolidation. Intrapulmonary vessels and bronchi are not unusual. Hilar nodes are numerous and some are large, soft and edematous. Nodes also extend along the great vessels and along the trachea and bronchi. On section, many of the nodes contain anthracotic pigment and scattered gray areas. A few are hemorrhagic.

Heart. Weighs 350 gm. Pericardial sac is thin-walled and smooth; it contains about 50 cc. of straw-colored fluid. Heart is hypertrophied and slightly flabby; the left side is prominent. On opening the chambers no thrombi or emboli are found. The left ventricle is dilated. There is considerable subendocardial fibrosis over the posterior and septal walls of the left ventricle. There are some small hemorrhages in the myocardium. Chordæ tendineæ are fairly prominent in right ventricle and somewhat flattened in the left. Posterior mitral valve flap has a markedly rolled edge. Aortic valve shows considerable atherosclerosis with calcification. There is a slight tendency to fusion in the region of the commissures. Coronary ostia are patent. There is considerable atherosclerosis with calcification in the larger branches of the coronary vessels, but no occlusion can be found.

Aorta. There is atherosclerosis in the region of the sinuses of Valsalva and around the coronary orifices. Remainder of the ascending arch of the upper descending aorta shows only scattered evidence of atherosclerosis. In the lower descending aorta atherosclerosis becomes prominent with considerable calcification, and the external iliacs are rigid tubes, showing a ring-like sclerosis of Mönckeberg. Orifices of main visceral branches of the aorta also show considerable calcification but the main renal arteries are relatively free from atherosclerosis.

Liver. Weighs 2100 gm. The entire left lobe is replaced by a mass of tumor tissue; and another similar mass 4 cm. in diameter is seen in the right lobe. Vena cava, portal vein and hepatic ducts run into the liver completely unobstructed, even in the region replaced by tumor. Gall bladder is normal.

Pancreas. Of average size and shape and deeply buried in dense fascia and adipose tissue.

Spleen: Weighs 1050 gm. The capsule is smooth except for a few very small areas of roughening. On section, cut surface is shiny and purplish with a homogeneous appearance. Architecture cannot be distinguished. Test for amyloid is negative. Splenic artery shows in places considerable atherosclerosis of the Mönckeberg type. Celiac axis and some of the other abdominal vessels are similarly involved, all showing marked calcification.

Suprarenals: Together weigh 23 gm. They are moderately firm. Cortex appears normal and contains a moderate amount of lipid. Medulla is reddish-gray and prominent.

Gastro-intestinal Tract: Shows nothing unusual.

Kidneys: Weigh 220 (right) and 225 (left) gm. Both are large. Capsules are firmly adherent to the perirenal fascia and fat. Capsule of *right kidney* strips with ease, revealing a slightly granular surface which has a pale-pink color. The right kidney's cut surface stands up slightly from the cut edge. Cortex and medulla are not well demarcated. Larger vessels in kidney substance show considerable sclerosis with calcification. *Left kidney:* Capsule also strips with ease but is much smoother and more purplish than the right. Corticomedullary junction is much more distinct than in right kidney. Cut surface tends to remain on a level with cut edge but larger vessels also contain calcium. *Prostate:* Very small and fairly soft. Seminal vesicles not unusual. *Testes:* Small, together weighing 19 gm. with the epididymes. They are soft, have a wrinkled tunica and on section are tan. Tubules string easily. Epididymes, on section, reveal little pigmentation.

Bone. (1). Marrow of lumbar vertebræ is red and appears normally trabeculated. 2. Incision made into right knee joint. Patella is somewhat roughened and there is a moderate amount of mucoid fluid in the cavity of the knee joint. 3. The periosteum over lower portion of femur is heavy and fibrous. Section of this portion of bone reveals a very thin cortex with an extensive spongy marrow, having a rather pale pink color.

Brain: Weighs 1250 gm. Scalp, calvarium and dura are normal. There is no congestion or thickening of the meninges. Vessels at base of brain are not sclerotic.

Spinal Cord: No abnormalities noted.

Microscopic Examination: Heart. Both ventricles show hypertrophy of muscle fibers with scattered areas of replacement fibrosis. In the posterior wall of the left ventricle there are a few areas of more recent infarction.

Lungs: Both lungs show emphysema and partial atelectasis. Many alveoli contain mononuclears and macrophages.

Liver: Portion of tumor is composed of branching cords and clumps of polygonal cells with round or oval hyperchromatic nuclei containing one or more nuclei. Between the cords there are strands of areolar tissue containing round cells and connective tissue cells. This portion of the tumor closely resembles liver tissue. There are also large areas of necrosis. Surrounding liver shows cloudy swelling. Portal areas shows round cell infiltration and there seems to be some proliferation of bile ducts.

Spleen: Marked fibrosis (Banti type) with considerable diminution in pulp and very small atrophic follicles and trabeculae.

Pancreas: Extensive autolysis of acinar tissue. Some of the islets are fairly large and irregular.

Kidneys: Increase in interstitial connective tissue to the point of actual scarring in areas. Glomeruli are anemic, some are hyalinized and show ring-like fibrosis around Bowman's capsule. There is broadening and hyalinization of walls of glomerular capillaries. Some of the tubules are dilated and contain hyaline casts, some contain calcium deposits. Arteriolar narrowing is seen. A moderate sized vessel shows intimal thickening.

Adrenal: Capsule uniformly thickened. Cortex is wide and moderately rich in lipid. Glomerular zone is active and well preserved, and there are numerous small circumscribed adenoma-like areas, for the most part composed of cells similar to those of the glomerular zone. Fascicular zone is fairly rich in lipid, well preserved, and many of the cells contain brownish pigment which is still more marked in the reticular zone. In addition there are several areas where these cells appear swollen, acidophilic and the nuclei are much enlarged and the stroma irregular. The medulla is well preserved, stains moderately with chrome salts and shows an occasional ill-defined focus of lymphocytes.

Thyroid. Multiple encapsulated colloid adenomata with some increase of stroma in the non-edeinatus areas. These adenomata are composed of very large and very small follicles most of which are distended with a rather homogeneous colloid.

Testis: Complete atrophy. Tubules small, thick walled, and for most part lined with a single layer of columnar epithelium. A few tubules contain distorted spermatogonia, but no spermatids. Interstitial cells are possibly relatively decreased, for despite the enormous atrophy of the tubules, there is no increase in the number per field. The individual cells, however, are intact, and many of them slightly pigmented. Epididymis appear normal, except that the tubules are free from sperm.

Prostate: Histologically, the acini are somewhat smaller than normal, many showing extensive desquamation of epithelial cells and round-cell infiltration in the submucosa. Fibromuscular stroma relatively increased.

Seminal Vesicles: Small. Glandular acini well preserved. Musculature relatively thickened.

Parathyroid: Markedly congested. No large clumps, but several scattered individual oxyphil cells are seen. For the most part the column of cells are large, with pinkish staining cytoplasm, so-called dark chief cells, but in other areas there is an increase in the cells whose cytoplasm is large, water clear and vacuolated, indicating increased activity.

Pituitary: Within normal limits. Normal eosinophil, basophil and chromophobe cells.

Pineal: Degenerated structure with scattered psammoma bodies.

*Summary of Endocrine Changes:** The testes, seminal vesicles and prostate gland are small. The aspermatogenesis and atrophy of the testes are premature. The adrenals are large with multiple cortical adenomata; the glomerular zone is active (whereas the glomerular zone in older people is usually ill-defined). The thyroid must have passed through cycles of increased and decreased activity to account for the multiple adenomata. The pituitary showed no abnormality. Parathyroids showed increased activity.

Femoral Artery: Marked calcification of the media (Mönckeberg sclerosis). Intimal thickening is also present.

Toe: Small artery shows marked ring-like calcification in the media, just below the internal elastic lamina. The epithelium shows some hyperkeratosis.

Skin. 1, Abdomen: Corium not dense. The corium appears of normal thickness, and the bundles of collagen fibrils loosely arranged stain a pale pinkish hue. Sweat glands appear normal in number and distribution. The epidermis is everywhere thinner than normal and covered with a thin layer of keratinized cells. The papillae are flattened out, greatly reduced in number and in depth. There is no, or very slight, pigmentation of the basal area.

2. Right knee: In addition to the foregoing there is dense round-cell and fibroblastic infiltration in areas. Neutrophils are also seen in these areas. Irregular blood and lymph channels are numerous (telangiectasia).

Brain. Abstract of postmortem report of Dr. Charles Davison. The macroscopic examination of the brain showed it to be markedly anemic. The vessels at the base were empty and normal. The microscopic examination revealed very little change except a loss of pigment granules in some of the hypothalamic nerve cells. In some regions the lateral hypothalamic nerve cells showed loss of chromatin material. The blood vessels showed no particular changes. Sections of the medulla oblongata and spinal cord showed no abnormality.

Anatomical Diagnosis. Werner's syndrome (clinical); diabetes mellitus (clinical); medial arteriosclerosis (Mönckeberg type) of visceral and peripheral arteries; calcification of mitral and aortic valves; atherosclerosis of coronary arteries; infarct, healed and recent, posterior wall of left ventricle and adjacent septum; cardiac hypertrophy; dilatation of left ventricle (type); ascites; status after abdominal paracentesis; ulcers of feet; status after amputation of large toe (right) and small toe (left); status after cataract extraction, bilateral; status after iridectomy, right; hyperactivity of parathyroid glands; osteoporosis, generalized; metastatic calcification, moderate, in skin, kidneys and vessels; atrophy of testes; scleroderma.

CASE 3 (Fig. 6), H. T. A Hungarian who had lived in New York for 35 years, was first admitted to this Hospital on August 6, 1938. He was 38 years of age, having been born on March 10, 1900.

Family History. His parents, Hungarians, were first cousins. Father died at the age of 35 of tumor of the neck. His mother is alive and well. Two brothers died in infancy, cause unknown. No sisters. His father's sister's daughter has parents who are first cousins; she has very small extremities. He has one son 8½ years old, who is well.

Patient was born in Hungary in a district not far removed from the ancestors of Patients 1 and 2, but not related as far as could be ascertained.

* For the histologic examination of the endocrine organs we are especially indebted to Dr. David Mainie.

Personal History. He is Jewish and had been a bookkeeper and cashier. He had had 7 admissions to other New York hospitals. He was well until 1926, although he had always had small extremities and the skin was



FIG. 6.—Case 3. Werner's syndrome. Amputation of arm not for Werner's syndrome but for fibro-sarcoma.

always tight especially over his hands and feet. In 1926 he suffered an injury to his left heel causing considerable pain and disability. An operation was performed resulting in a foot drop. He developed various cracks in the skin of the foot which took a long time to heal. By 1927 he had ulcer-

of the left foot with shortening of the Achilles tendon. In July, 1937, he had an ulcer of the right heel. The toes of his feet gradually became immovable, and the skin became hard, dry and shiny. In September, 1936, he had to have two phalanges of his left fourth finger amputated after having caught the finger in a door. In 1938 an advanced sclerosis of the blood vessels of the upper and lower extremities was noticed; also a moderate demineralization of the entire osseous system. He also had graying of the hair beginning in 1918, loss of hair in 1923, loosening of the teeth beginning in 1933, cataracts appearing in 1931, requiring a left iridectomy in 1932 and a right iridectomy in 1937.

In 1937 he first noticed a swelling of his left forearm, which on Roentgen ray revealed an erosion of the radius. This mass, removed in 1938, was diagnosed histologically as a fibrosarcoma.

Physical Examination. He was undersized. Although actually 38 years of age, he was generally taken for 55. His height was 157 cm. and his weight 52 kg. He was gray and partly bald. His teeth were carious, many were broken or missing. Extremities were gracile, the torso large. His eyes were prominent and staring, the sclerae were blue. Bilateral postoperative coloboma of the iris, aphakia of the left eye, and cataract of the right lens were found. Voice was high-pitched. There were prominent veins over the thorax and extremities, severe ulcerations and pigmentation of both feet. Gynecomastia was present to a mild degree. The hair over the abdomen and chest was sparse. The genitalia were small. The distribution of the pubic hair was feminine in type. Both testes were small; the left especially so. The lungs were clear. The heart was not enlarged; there was a systolic murmur over the aortic area. Blood pressure was 180/108. Abdominal examination disclosed no enlargement of any of the viscera. Prostate was very small and smooth, and felt about one-third normal size. No lymphadenopathy except for two small nodes in the right axilla. Extremities were small and slender. The skin was drawn tightly over the shins and wrists, and presented many areas of pigmentation, discoloration and dry scales. There were a few telangiectases of the skin over the knees and face, a foul-smelling necrotic mass overlying the left radius, pressure atrophy over the right elbow, a crusted ulcer over the right malleolus. The skin of the toes was dry, hard and so taut that the toes could not be moved. No pulsation of the dorsalis pedis or posterior tibial arteries could be felt. The left ankle was fixed in extension, the knee could not be fully extended, the right ankle had slight power and movement. Circumference of left leg was smaller than the right. The arteries of the extremities felt sclerotic. Scleroderma and sclerodactylia were present.

Neurologic Examination. There were no cranial nerve changes. All deep reflexes were exaggerated. Spontaneous ankle clonus on the right side was sustained. Marked plantar hyperesthesia, bilaterally, but no hyperesthesia of the calves. The plantar reflexes were normal. Abdominal and cremasteric reflexes were equal and active.

Laboratory Data. The electrocardiogram showed only a left axis deviation. Basal metabolic rate was -8% and -5% . Urine: acid, 1020, many leukocytes, otherwise no abnormality. Blood examination: Hemoglobin 110%; red blood cell count 5,950,000; leukocyte count 5,750 (neutrophils, 65%, lymphocytes, 35%). Blood urea nitrogen 12 mg. per 100 cc.; sugar 87, cholesterol 167, cholesterol esters 111. Glucose tolerance test: fasting 87 mg. per 100 cc., after $\frac{1}{2}$ hour, 141; 1 hour, 154; 2 hours, 72; 3 hours, 80; 4 hours, 85. Blood Wassermann and Kahn tests negative. Positive Hamilton test for parathormone (Baumann and Sprinson). The blood serum calcium was 10.3 mg. per 100 cc., serum phosphorus 3.9 mg. per 100 cc. The phosphatase was 6 Bodansky units per 100 cc. (Dr. M. Sandberg). The CO_2 combining power was 60.6 vol. %. Roentgen ray

examination revealed a generalized osteoporosis; calcification of the blood vessels; a normal sella turcica. On February 20, 1940, analysis of the skin dissected from the areolar tissue revealed: water 54.4%, calcium 9.7 mg. per 100 cc. wet, 21.3 mg. per 100 cc. dry (Dr. E. J. Baumann).

Course. The cataract of the right eye was removed by Dr. Agatston¹ on October 10, 1938. The fundus was normal with the exception of senile arteriolosclerosis with slight hypertensive changes. The patient also received very intensive Roentgen ray treatment to the tumor of the left forearm; but finally a flap amputation through the upper third of the left arm had to be performed. The stump healed well. He was placed on dihydro-tachysterol for the scleroderma, with subjective improvement. Nevertheless at the time of his discharge from hospital, and even as late as May, 1941, he was unable to stand or walk without crutches because of the scleroderma and deformity of his lower extremities (Fig. 6).

TABLE 1.—TABULATED FINDINGS IN 3 PATIENTS.

D. G., age 48 years.	A. G., died 42 years.	H. T., age 41 years.
Premature graying and baldness (12)*	Premature graying and baldness (8)	Premature graying and baldness (18)
Scleroderma (28)	Scleroderma (34)	Scleroderma (26)
Precocious cataracts (36)	Precocious cataracts (29)	Precocious cataracts (32)
Characteristic habitus	Characteristic habitus	Characteristic habitus
Hypogonadism	Hypogonadism	Hypogonadism
Trophic ulcers, legs	Trophic ulcers, legs	Trophic ulcers
Normal sclerae	Blue sclerae	Blue sclerae
Metastatic calcification	Metastatic calcification	Metastatic calcification
Osteoporosis	Osteoporosis	Osteoporosis
Calcification of vessels	Calcification of vessels	Calcification of vessels
Hypoglycemic tendency	Diabetes mellitus	Borderline hypoglycemia
No neoplasm	Primary cancer of liver	Fibrosarcoma of radius
Normal calcium balance	Negative calcium balance	Blood calcium normal
Hamilton test: normal	Hamilton test: positive	Hamilton test: positive

* These figures indicate the age of onset of the respective signs and symptoms.

The outstanding features of our 3 cases are summarized in Table 1. The prominent clinical symptoms are referable to structures ectodermal in origin. The canities appears generally in the second decade of life, premature loss of hair somewhat later, the sclero-poikiloderma in the third decade, and the bilateral juvenile cataract rather early in the fourth decade. Heredity and consanguinity play an important rôle, suggesting that the ectodermal abnormalities represent an abiotrophy. It is of interest that two unusual types of primary malignant tumors have occurred in 2 out of our 3 cases, and in both instances at a relatively early age.

The cases clinically presented endocrine stigmatization in which we were particularly interested. Attention has already been called to the participation of the gonads. In the male, hypogonitalism, delayed puberty, failure of full development of the secondary sexual characters, occasional gynecomastia, large broad pelvis and eunuchoid appearance have been noted. In the reported female cases, there is evidence of ovarian insufficiency in delayed puberty, infrequent or scanty menstruation, or irregular menstruation, with subsequent premature amenorrhea occurring as early as the sixteenth year. Increased urinary excretion of folliculin has been reported by

Marchionini and Lux.⁵ In the latter case attention was called to the transient hypofunction of the islet tissue of the pancreas in that the glucose tolerance test occasionally revealed a diabetic type of curve. Of our patients, Case 2 was a frank diabetic, Case 1 had a hypoglycemic tendency, and Case 3 also presented a borderline hypoglycemia. Disturbances of the thyroid gland, such as goiter, or frank Graves' disease, or merely Basedowian symptoms, have been repeatedly described in the patients themselves or in members of their family. In 2 of our 3 cases the eyes were prominent, but the basal metabolic rates were rather subnormal; the postmortem examination of one thyroid gland revealed multiple adenomata. This necropsy also showed adrenal cortical adenomata, with evidence of activity of the glomerular zone. Careful examination of the pituitary did not reveal any histologic abnormalities.

In the original communication attention was called to the participation of the parathyroid gland. Subsequent observations have yielded more evidence for this view. The following findings are suggestive of hyperparathyroid effects in Werner's syndrome:

1. Generalized and localized osteoporosis.
2. Metastatic calcification as indicated in: *a*, the arterial tree; advanced and extensive Mönckeberg's sclerosis at a relatively early age; *b*, phleboliths; *c*, calcific deposits in the soft tissues (ligaments, skin, kidneys).
3. Transient, recurrent hypercalcemia.
4. Abnormal negative calcium balance in at least 1 case.
5. Increased circulating parathormone (by the Hamilton test) in 2 of 3 cases.

Moreover, observations on the relationship of scleroderma to hyperparathyroidism, to which we have previously referred, have recently been extended by the clinical and experimental investigations of Selye,⁷ and of Leriche and Jung.⁴

The validity of the test of Hamilton and Schwartz³ for parathormone, positive in 2 of our 3 cases, has been confirmed by Baumann and Sprinson.²

Treatment. Removal of the fully developed cataracts has successfully restored vision. Amputation of both legs has been necessary in one instance. Dihydrotachysterol (A.T.10) gave subjective improvement. Other than those measures, treatment, as in so many other heredofamilial disorders, was unsatisfactory.

Summary. 1. Werner's syndrome may be defined as a rare heredofamilial disorder with sclero-poikiloderma, bilateral juvenile cataract, canities, laryngeal changes, endocrine stigmatization of a pluriglandular type and constitutional inferiority.

2. Three cases of Werner's syndrome including the first reported necropsy are reviewed.

3. The clinical evidence of endocrine stigmatization was confirmed by the following post-mortem findings: atrophy of the testes

and prostate gland, adenomata of the thyroid and adrenal, and evidence of hyperactivity of the parathyroid. The pituitary gland showed no abnormalities.

4. The clinical evidences of parathyroid hyper-activity are enumerated, and their significance briefly discussed.

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THE HAMILTON-SCHWARTZ TEST AND HYPERPARATHYROIDISM IN VARIOUS DISEASES.

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In 1932, Hamilton and Schwartz^{6a,b} reported a method for determining small amounts of parathyroid hormone in blood or extracts by producing a characteristic blood calcium curve in rabbits following oral administration of calcium chloride. In 1936, with the use of this method, Hamilton and Highman⁵ established the parathyroid hormone level in 38 normal individuals and concluded that a minimum rise of 0.3 millimols (1.2 mg. per 100 cc.) of calcium per liter or higher was indicative of excessive amounts of hormone.

The method was then applied to various disorders where hyperparathyroidism was suspected. In the study of rickets, first, experimentally, Hamilton and Schwartz^{6c} found that of 12 rachitic animals, 9 gave positive tests indicating excessive amounts of hormone; then, clinically, Highman and Hamilton^{5a} and Kajdi and Shelling¹¹ each reported a rachitic patient positive. Several studies were made in kidney disease. Shelling and Remsen¹⁸ reported a positive test in a case of renal rickets which, at autopsy, revealed enlarged parathyroid glands. Bass and Pakter² reported a questionably positive and a negative test in a case of polycystic kidney with bone changes. Highman and Hamilton^{5b} reported positive tests in 20 of 23 cases of chronic nephritis, while Gilligan, Volk and Gargill⁴ found but 1 of 15 such cases positive, even though 4 of those with negative results had enlarged parathyroid glands at autopsy. In other diseases Kajdi and Shelling¹¹ reported a case of osteitis fibrosa cystica positive and 1 of xanthomatosis and 1 of Paget's disease

negative. Gilligan, Volk and Gargill,⁴ on the other hand, found 3 of 8 cases of Paget's disease positive. The latter authors also reported 7 of 18 cases of thyrotoxicosis positive, 2 of the positive patients turning negative after iodine therapy. Studying the state of the parathyroid gland in pregnancy, Hamilton, DaSef, Highman and Schwartz⁷ found the hormone level excessive, especially between the 15th and 35th week. This corresponds with the changes in the histology of the gland.^{9,10,14a,16,17} Finally, a closer correlation between the parathyroid gland and the Hamilton-Schwartz (H-S) test was recently established experimentally by Baumann and Sprinson.^{3a} With varying degrees of parathyroid enlargement (feeding rabbits a high phosphorus diet over a prolonged period) there was close correspondence between the H-S test and the degree of hyperplasia observed histologically. Positive tests were obtained in these animals for as long as $2\frac{1}{2}$ years. They further noted^{3b} that the use of a proper strain of animal is essential for the success of the test since the Dutch, Belgian and hybrids of these two varieties are less resistant than the New Zealand whites and chinchillas.

PURPOSE OF STUDY. We have made an attempt to detect excessive amounts of parathyroid hormone by means of the H-S test in various clinical disorders in which increased parathyroid activity was suspected, especially where not reflected by abnormality in the blood calcium and phosphorus levels. Further, wherever possible, the parathyroid gland was studied histologically for correlation between changes in structure and the H-S test.

Method. The test was made according to the modified method of Hamilton and Highman:⁵ 100 mg. of calcium as calcium chloride in 10 cc. water was given to a properly controlled rabbit (see below) by stomach tube at the beginning of the test and again at 1, 3 and 5 hours. Thirty cubic centimeters of blood was drawn from the patient and 15 cc. injected immediately into each thigh muscle of the animal. Blood was drawn from the animal at the beginning of the test and 7 to 15 minutes after the last two administrations of calcium chloride. Excessive parathyroid hormone was indicated by a minimum rise of blood calcium of 0.3 millimols per liter after either the 3d or 4th administration of calcium chloride, usually somewhat sustained at the end of 3 to 5 hours. The rabbits used were of the Dutch and Belgian strains and at least 5 months old. They were fed on an alfalfa and oats diet with a Ca:P ratio of at least 1:1. A control test was carried out on the animal 4 to 5 days before studying a patient by following the blood calcium curve with the administration of calcium chloride alone obtaining a negative result. Rarely, the animal was controlled by administering 20 units. parathormone and obtaining a positive result with calcium chloride.

Results (Table 1). Because of the unique character of many of the cases studied, it is believed best to present the results in reference to the particular case.

GROUP 1. HYPERPARATHYROIDISM. *Case 1* had had a parathyroid adenoma, 3 cm. in diameter, removed 6 months before the test. At the time of the H-S test, there was still extensive osteoporosis

with cystic formation though some improvement in bone density was noted since operation. Though the blood Ca-P levels were normal (Ca 9.6 mg. per 100 cc.; P 2.4 mg. per 100 cc.; phosphatase 27.9 Bu*), the H-S test was markedly positive. Microscopically, the gland was composed largely of the "water-clear" cell type and a clump of suggestively malignant cells were noted in the lumen of a vessel. A follow-up note from the Presbyterian Hospital revealed that recently, following the recurrence of signs and symptoms, a second operation revealed two nodules of parathyroid-like tissue. This was diagnosed as a carcinoma of the parathyroid gland.

TABLE 1.—RESULTS OF THE HAMILTON-SCHWARTZ TEST IN VARIOUS DISEASES WITH HISTOLOGIC EXAMINATION OF THE PARATHYROID GLAND IN SOME.

Disease.	No cases	H-S test		Parathyroid histology	
		Pos	Neg	Active	Resting
Hyperparathyroidism	2	2	0	2	0
Werner's syndrome	3	2	1	1	0
Paget's disease	5	3	2	1	0
Chronic renal disease	8	2	6	3	0
Scleroderma†	2	0	2	0	0
Osteitis fibrosa disseminata	1	0	1	1‡	0
Cushing's syndrome	1	0	1	0	0
Multiple myeloma	1	0	1	1‡	0
Arthritis	3	0	3	0	0
Edema with hypocalcemia	1	0	1	1‡	0
Posthyperecalcemia	1	0	1	0	0
Renal calculi	1	0	1	0	0
Hypogonadism	1	0	1	0	0
Osteogenesis imperfecta	1	0	1	0	0

Case 2, roentgenographically, revealed diffuse resorption of bone calcium without cystic formation. The blood P was persistently low (1.8 mg. per 100 cc.) while the Ca was normal (10.8 mg. per 100 cc.). Phosphatase was 7 Bu. The H-S test was positive. An exploratory operation revealed no parathyroid adenoma though a gland removed showed scattered areas of "water-clear" cells, microscopically, indicative of hyperactivity.

GROUP 2. PLURIGLANDULAR SYNDROME. *Cases 1, 2 and 3* (H. T. being reported elsewhere) represent a rare clinical entity—that of Werner's syndrome. Two of these cases, brothers, A. G., and D. G., have previously been reported by Oppenheimer and Kugel.¹⁵ The syndrome is briefly characterized by them as a "rare heredofamilial disorder with sclerodermatous or poikilodermatous skin changes, bilateral juvenile cataract, canities, laryngeal changes, endocrine stigmatization of a pluriglandular type and evidence of constitutional physical inferiority." Metabolic studies had revealed a negative calcium balance in 1 of the patients (A. G.) suggesting increased parathyroid activity. In the present study, at the time of the H-S test, A. G. had a blood Ca of 12 mg. per 100 cc. and P of

* Bodansky units.

† See text for discussion of parathyroid gland biopsy.

‡ Activity not striking though present.

3 mg. per 100 cc. The phosphatase was 8 Bu. The H-S test was positive. This patient subsequently came to autopsy (being reported at length elsewhere) with a terminal blood Ca level of 13.1 mg. per 100 cc. The parathyroid gland, though not particularly enlarged, presented areas of "water-clear" cells intermingled with areas of fibrosis suggesting repeated phases of activity and remissions in the past.^{14b} The other of the two brothers, D. G., had normal blood Ca-P-phosphatase levels and a negative H-S test. This patient had previously had a normal calcium balance.¹⁵ The 3d case, H. T.,

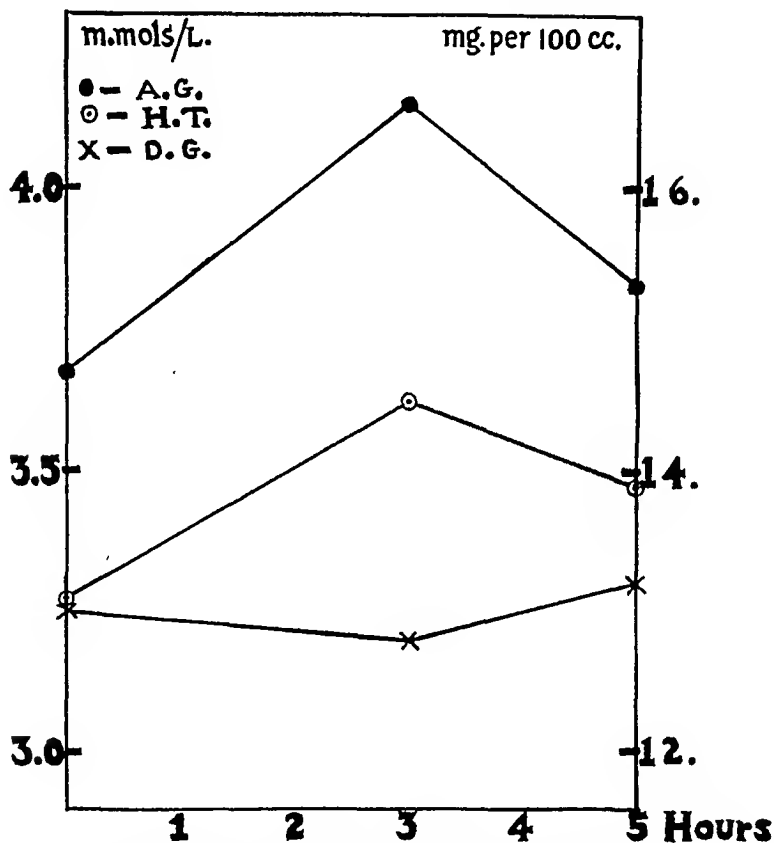


CHART 1.—Hamilton-Schwartz test in 3 cases of Werner's syndrome. The chart shows a rise of more than 1.2 mg. per 100 cc. calcium in the rabbit blood in 3 hours and sustained above the initial level in 5 hours according to the method of Hamilton and Schwartz in 2 of 3 cases of Werner's syndrome.

had normal blood Ca-P-phosphatase levels (Ca 10.3 mg. per 100 cc.; P 3.9 mg. per 100 cc.; phosphatase 6 Bu). The H-S test was positive.

Case 4 was one of osteitis fibrosa disseminata in a 12-year-old white female previously reported by McCune and Bruch¹³ and the syndrome discussed at length by Albright, Butler, Hampton and Smith.¹ The case is characterized as one of precocious puberty, skin pigmentation, asymmetrical bone changes with cyst-like forma-

tion not too unlike von Recklinghausen's disease, and elevated basal metabolic rate. Despite the suspected increased parathyroid activity, repeated blood Ca and P levels were normal (Ca 9.6 mg. per 100 cc.; P 2.3 mg. per 100 cc.; phosphatase 0.21 Ku (Kay units). The H-S test was negative. At autopsy, the parathyroid gland showed some evidence of increased activity, though not strikingly so. The thyroid gland, on the other hand, was distinctly hyperactive. The autopsy is being reported in full elsewhere.

Case 5 was one of Cushing's syndrome of 19 years' standing with severe osteoporosis and collapse of several vertebræ. There had been considerable improvement in the clinical picture with increased calcium deposition in the bones during the past 4 years. At the time of the H-S test, the blood Ca-P levels were normal (Ca 10.5 mg. per 100 cc.; P 3.3 mg. per 100 cc.) and the test was negative which was in accord with the improved clinical status.

Case 6 presented the chief complaints of muscle weakness of long-standing and recent anigal seizures and dyspnea. There was known testicular atrophy and loss of libido for many years and evidence of hypothyroidism indicated by repeatedly low basal metabolic rate determinations. The blood Ca-P levels were normal and the H-S test negative which was in accord with the generally depressed endocrine state.

GROUP 3. PAGET'S DISEASE. Five cases of Paget's disease were studied, all characterized by a history of many years' duration and extensive bone involvement. One case had an associated osteogenic sarcoma. The blood Ca-P levels in all cases were normal, nevertheless, the H-S test was definitely positive in 2 and questionably so in a third case. The case with the associated sarcoma eventually came to autopsy and showed slight gross enlargement with many localized areas of "water-clear" cells, microscopically, indicating hyperactivity. This case had had a definitely positive H-S test.

GROUP 4. CHRONIC GLOMERULONEPHRITIS. Of 8 cases of chronic glomerulonephritis studied, 2, both in uremia, gave borderline positive tests. One showed a progressive rise to 1 mg. per 100 cc. with the peak in 5 hours, the other, 1.1 mg. per 100 cc. in 3 hours when the animal died. In both cases there was inversion of the blood Ca-P levels, clinically. At autopsy, 1 case showed slight enlargement of the parathyroid glands and both showed areas of "water-clear" cells indicative of hyperactivity. A third case with a normal blood Ca-P level had a negative H-S test. However, 1 year later, at autopsy, one parathyroid gland was enlarged, measuring 1 cm. in diameter, and showed a predominance of the clear chief-cell type and areas of "water-clear" cells. The only other instance of an altered blood Ca-P level and a negative H-S test was a case with an initial history of chronic rheumatic heart disease terminating in

congestive failure and uremia of short duration. No autopsy was obtained.

GROUP 5. SCLERODERMA. Two cases of scleroderma were studied in view of the questionable rôle played by the parathyroid gland in its pathogenesis. Both cases were long-standing and neither showed abnormal blood Ca-P levels. The H-S test in both was negative. It is noteworthy, however, that one of these cases had had a parathyroidectomy as a vain therapeutic measure 2 years before when there was marked histologic evidence of hyperactivity. This patient came to autopsy several months after the H-S test following the development of a severe mediastinitis. The thyroid-parathyroid region was markedly fibrosed so that no parathyroid tissue was found.

GROUP 6. ARTHRITIS. This group consisted of 3 cases, 2 being that of Still's disease studied because of severe osteoporosis with markedly deforming arthritis. At the time of the H-S test, both cases were well in the chronic phase and improving. The blood Ca-P levels were normal. The test was negative. The third case was that of a moderate rheumatoid arthritis with slight bone calcium resorption associated with rapid growth of questionable endocrine origin and an admission report of slightly elevated blood calcium level. At the time of the H-S test, the blood calcium level was normal, while the test was borderline. A repeat test proved negative.

GROUP 7. MISCELLANEOUS. *Multiple Myeloma.* This patient presented the characteristic bone changes and Bence-Jones proteinuria. The blood Ca-P levels were normal. The H-S test was negative. At autopsy, the parathyroid glands suggested some activity, though not strikingly so.

Edema of Unknown Origin. The essential clinical features were marked hypoproteinemia, hypocalcemia and edema for 21 years with sporadic asthmatic (?) seizures and, more recently, cardiac failure. In view of the marked depression in blood calcium level, it was thought possible to detect increased circulating parathyroid hormone due to compensatory increased parathyroid activity. However, the H-S test was negative. At autopsy, 1 year later, the parathyroid glands showed suggestive though not striking evidence of increased activity.

Posthypercalcemia. This patient had an attack resembling renal colic 1 year before the H-S test but not confirmed by roentgenogram. The blood calcium then was 14.2 mg. per 100 cc. and phosphorus 5.7 mg. per 100 cc. Eight months later, the calcium was still 13.2 mg. per 100 cc. when sodium citrate therapy was begun. At the time of the H-S test the Ca-P level was normal. The test was negative.

Recurrent Renal Calculi. The H-S test was made to rule out hyperparathyroidism as the possible etiology of recurrent renal

calculi in spite of the repeated normal blood Ca-P levels. The test was negative.

Osteogenesis Imperfecta. This case was that of a child with the characteristic bone changes of osteogenesis imperfecta for 7 years and a history of numerous fractures. The blood Ca-P levels were persistently normal. The H-S test was negative.

Comment. There are several noteworthy observations from the data presented above. First, apart from the 2 cases of chronic nephritis, whose altered blood Ca-P levels are attributed essentially to underlying renal disease, 6 of the 7 cases with positive H-S tests had normal blood levels for both Ca and P, at the time of examination. In the 7th case (Case 2, Group 1) only the P level was persistently low. The parathyroid glands in 3 of the 6 cases were examined histologically and activity confirmed: This appears significant and indicates the considerable aid the H-S test might offer in diagnosis particularly where routine blood examination reflects no parathyroid gland disturbance.

Second, the close correlation between the H-S test and the histologic appearance of the parathyroid gland appears striking. In all 6 cases where the parathyroid glands were examined and the H-S test was previously positive, the hyperactivity of the glands was confirmed histologically. In the other 4 cases where the parathyroid glands were examined and the H-S test was previously negative, the histologic evidence of activity in all but 1 was not striking, if any more than suggestive. The exception was the case of chronic nephritis with the parathyroid adenoma and moderately active appearance. However, the parathyroid glands in this case, as those of 1 of the other 3 cases, were examined 1 year after the test so that proper correlation is difficult.

In view of the otherwise generally close correlation between the H-S test and the appearance of the parathyroid gland, the probable significance of the test in the interpretation of several of the diseases studied becomes apparent. First, in Paget's disease, it is noteworthy that 2 and possibly 3 of the 5 cases studied had a positive H-S test. This is in accord with Gilligan, Volk and Gargill,⁴ who reported 3 of 8 cases positive, particularly significant, since they could find but 1 of 15 cases of chronic renal disease positive. This suggests the possible rôle of the parathyroid gland in the pathogenesis of Paget's disease, whether acting alone or in combination with other members of the endocrine system. On the other hand, it must be noted that 1 of the positive cases in the present series, confirmed histologically, had an associated osteogenic sarcoma, which, in itself, may produce an actively appearing gland.¹² Second, in Werner's syndrome, the results of the H-S test are striking—2 of 3 cases being distinctly positive and 1 confirmed histologically. These results, in conjunction with the observation of a negative calcium balance and hypercalcemia in the autopsied case previously

made by Oppenheimer and Kugel,¹⁵ lend further support to the rôle of the parathyroid gland in the pathogenesis of the disease.

On the other hand, negative results may also be significant. This appears true in the case of osteitis fibrosa disseminata (Group 2, Case 4). McCune and Bruch¹³ in their study of this same case several years before reported positive calcium balance studies and several negative H-S tests. In the present study, the H-S test was again negative and subsequent autopsy revealed the parathyroid gland to have some but no striking activity. This would tend to exclude the parathyroid gland as a major factor in the pathogenesis of the disease, in spite of the resemblance between the bone changes here and those of true von Recklinghausen's disease.

An explanation might be offered for the rare instances of a negative H-S test where the parathyroid gland was distinctly active, histologically, or for the negative test in the 1 case of Werner's syndrome where the other 2 cases were positive. It is felt that a remission phase of parathyroid gland function will produce a negative result even in the face of apparent hyperactivity, histologically. Evidence for such alternate phases of activity and remission appears present in the histologic appearance of the parathyroid gland of the 1 autopsied case of Werner's syndrome.^{14b}

Finally, it is thought that some of the discrepancies in results hitherto noted in the literature, such as those reported in chronic renal disease by Highman and Hamilton^{8b} and Gilligan, Volk and Gargill⁴ may perhaps be attributed to differences in control factors. The use of a strain of rabbit that is capable of response, such as the Dutch, Belgian and hybrids of the two varieties, in contradistinction to New Zealand whites and chinchillas, of an age that is at least 5 months and fed on a control diet with a Ca-P ratio of at least 1:1, are felt to be prerequisites for the application of the H-S test. Further, actual study of the patient should be preceded by control of the animal as to potential response. These various factors have been amply stressed by Baumann and Sprinson.^{3a,b}

Summary. An attempt was made to detect excessive amounts of circulating parathyroid hormone, as a reflection of increased parathyroid gland activity, in various diseases by means of the Hamilton-Schwartz (H-S) test. Histologic examination of the parathyroid gland was made wherever possible in order to establish a correlation between the test and degree of activity, histologically.

It was observed, first, that in practically all instances where the H-S test proved positive, the blood calcium-phosphorus levels were normal; second, that in most instances of histologic evidence of parathyroid gland activity, the H-S test was previously positive. Conversely, in all instances of positive H-S tests with subsequent histologic study, the parathyroid gland proved to be hyperactive. The data suggest a positive rôle of the parathyroid gland in the pathogenesis of Werner's syndrome and Paget's disease.

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A. NOTE ON THE EFFECT OF DERMAL AND ENTERAL IRRADIATION BY RADIO-PHOSPHORUS ON THE BLOOD LEVELS OF DOGS.

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Materials and Methods. Radio-phosphorus (P^{32}) produced by the Berkeley cyclotron,⁴ emits only beta particles (with energies averaging 600,000 electron-volts) which travel less than 0.8 cm distance in water. It has a half-life of 14.3 days. An amount of P^{32} was converted into sodium phosphate, which was dissolved in water. Of this hypertonic solution, 2.5 cc. was placed into each of 6 rubber capsules (finger cots sealed with rubber cement), which could be fed manually or applied to the skin. Each capsule emitted 5.5 millicuries of beta-radiation. (One millicurie = 37,000,000 beta particles per second.)

By puncturing the marginal ear veins of 4 healthy and active dogs (weighing from 6 to 7 kg), which had been wormed and acclimated to being housed in large wire bottomed cages, freely flowing blood was obtained for making complete blood counts. Pipettes standardized by the U. S. Bureau of Standards and an Osgood-Sahli hemoglobinometer were used. Blood counts were made before, during and after the administration of radiation.

A choice in the method of administration had to be made: (A) The capsules could be fed orally to some dogs and applied to the skin of others for a specified time period. A small localized area of skin would be irradiated constantly in the latter group; while much of the mucosa and submucosa, with their vascular systems, of the gastro-intestinal tract would be irradiated temporarily as the capsule passed through the lumen, in the

TABLE 1.—DETAILS OF BLOOD COUNTS.

	Doc I.						Doc IV.						Doc II.						Doc III.					
	No. of days after 12/12/40.	W.B.C., thousands	% of lymphocytes.	Absolute No. of lymphocytes.	% of neutrophils.	Absolute No. of neutrophils.	W.B.C., thousands	% of lymphocytes.	Absolute No. of lymphocytes.	% of neutrophils.	Absolute No. of neutrophils.	W.B.C., thousands	% of lymphocytes.	Absolute No. of lymphocytes.	% of neutrophils.	Absolute No. of lymphocytes.	W.B.C., thousands	% of lymphocytes.	Absolute No. of lymphocytes.	% of neutrophils.	Absolute No. of neutrophils.			
1	0	19 2	23	4420	66	12,700	23 3	19	4430	71	16,500	19 1	15	2870	65	12,500	25 0	13	3270	58	14,600			
2	2	12 1	30	5650	50	9,425	15 9	20	3050	64	9,760	23 6	12	3210	78	21,000	16 3	16	3040	53	10,100			
3	5	18 8	33	4540	53	7,290	15 3	14	2510	69	12,300	26 8	17	4610	75	20,400	19 0	22	5200	59	13,900			
4	7	13 7	26	3510	62	8,370	17 9	21	3000	66	9,450	27 2	19	4560	67	13,300	23 6	16	4160	63	16,400			
5	10	13 5	29	3300	50	5,700	14 3	24	4560	69	13,100	19 8	23	3330	78	17,300	26 0	20	4650	65	15,100			
6	17	11 4	27	4590	60	10,200	19 0	26	3150	55	6,650	22 2	15	3420	69	9,450	23 3	22	4310	60	11,800			
7	25	17 0	27	4590	60	10,200	12 1	26	3150	55	6,650	13 7	25	3420	69	9,450	19 6	22	4310	60	11,800			
8	30	16 5	20	3300	65	10,700	17 8	24	4270	60	10,700	20 1	23	4620	73	14,700	12 4	22	2730	62	7,690			
9	35	12 6	26	3280	63	7,950	12 4	31	3840	54	6,700	13 3	21	2790	84	11,200	22 0	27	5940	63	13,900			
10	40	16 8	30	5050	57	9,580	12 2	34	4150	52	6,350	12 1	23	2780	70	8,460	13 4	24	3210	58	7,760			
11	41	7 3	20	3300	56	4,080	8 3	17	1410	65	5,400	12 3	26	3200	61	7,500	15 8	14	2220	78	12,300			
12	42	18 3	25	4575	64	11,700	10 8	25	2700	60	6,490	10 4	27	2810	65	6,760	21 1	12	2540	84	17,700			
13	43	18 1	34	6150	52	9,410	11 4	15	1710	69	7,880	10 4	27	2810	67	6,970	14 4	16	2310	69	9,950			
14	44	15 4	36	5550	48	7,400	11 1	29	3220	51	5,660	9 9	30	2950	59	5,840	14 0	14	1960	70	9,800			
15	45	17 0	21	3570	59	10,000	11 1	10	1110	78	8,650	15 0	23	3450	68	10,200	17 8	13	2320	76	13,500			
16	47	12 3	22	2700	67	8,240	10 6	7	743	80	8,490	12 6	21	2640	68	8,560	12 8	23	2940	65	8,310			
17	48	11 3	30	3390	54	6,100	13 6	17	2310	73	9,920	14 8	18	2670	72	10,600	15 6	17	2650	72	11,200			
18	49	11 1	32	3650	51	5,660	7 9	21	1660	73	5,760	15 2	15	2280	79	12,000	11 7	23	2690	59	6,900			
19	50	17 2	24	4120	62	10,680	8 8	16	1410	72	6,330	13 9	18	2500	74	10,300	10 5	20	2100	68	7,150			
20	53	14 4	16	2310	72	10,400	9 1	15	1370	80	7,290	10 7	18	1930	76	8,150	13 7	13	1780	75	10,300			
21	55	14 7	30	4410	54	7,940	18 2	21	3820	68	12,400	8 0	17	1360	68	5,450	10 5	11	1160	76	7,990			
22	57	18 9	13	2460	76	14,400	21 2	20	4240	69	14,600	10 7	17	1820	68	7,270	13 4	13	1740	70	9,400			
23	60	21 3	13	2770	78	16,600	18 6	19	3540	70	13,000	13 6	28	3810	59	8,040	18 1	21	3800	59	10,700			
24	62	21 5	25	5380	66	14,200	17 6	15	2640	73	12,900	15 7	21	3300	69	10,800	13 4	20	2680	66	8,850			
25	61	25 3	18	4550	81	20,500	13 8	10	1380	81	11,200	10 4	22	2280	74	7,690	14 5	15	2180	69	10,000			
26	68	18 7	8	1500	89	16,600	19 7	17	3350	79	15,600	10 0	16	1600	78	7,800	16 1	14	2260	63	10,100			
27	74	12 4	22	2730	71	8,800	16 5	15	2480	76	12,500	11 5	28	3220	65	7,470	18 2	20	3640	56	10,200			
28	85	12 9	26	3360	58	7,500	18 6	16	2980	64	11,900	6 4	19	1220	67	4,280	11 7	20	2340	56	6,550			

Enteral irradiation.

Dermal irradiation.

former group. (B) Capsules could be fed orally to one group while an equal amount of radio-phosphorus mixed in an ointment could be applied to an area of shaved skin equal to the area of the gastro-intestinal mucosa. In neither A nor B could the factors of area and time be made comparable. Method A was chosen.

Experiment. To Dogs 2 and 3 a capsule was placed on the skin (after shaving) over the site of the spleen of each by the use of adhesive tape. The capsules were applied on Jan. 21, 1941, and removed on Feb. 1, 1941. To the others, Dogs 1 and 4, the capsules were administered orally by manual feeding. As soon as one capsule was excreted another was fed so that one capsule was in the gastro-intestinal tract of each dog at all times. It took between 16 to 24 hours for the capsules to travel the entire length of the gastro-intestinal tract. Capsules were fed 11 consecutive times to each dog from Jan. 21, 1941, to Feb. 1, 1941.

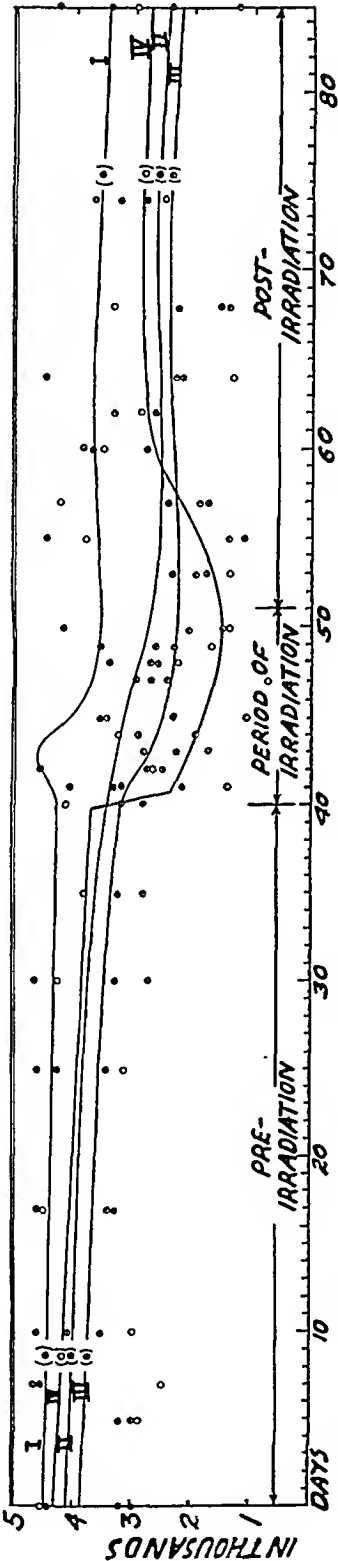
Results. The changes that occurred in the white blood cell levels and the absolute numbers of circulating lymphocytes and neutrophils of the 2 (Dogs 2 and 3) that received the same amounts of radiation applied to the skin, and in 2 others (Dogs 1 and 4) to whom equal amounts of radiation were applied to the gastro-intestinal tract through its lumen, are illustrated in Table 1.

The trends of the levels of the white blood cells were not consistent. Those of Dogs 2 and 3 did not vary significantly during the period of irradiation. However, there was a rise in the trend of Dog 3 but not of Dog 2 after the period of irradiation. That of Dog 1 rose immediately following the ingestion of the first few capsules, then fell below its base line; but following the cessation of irradiation it rose compensatorily above the base line. The trend of Dog 4 dropped immediately upon administration of the irradiation and remained low during the period of irradiation, but rose compensatorily above the base line after the period of irradiation.

The trends of the levels of the absolute numbers of neutrophils followed those of the white blood cells.

The trends of the levels of the absolute numbers of lymphocytes in Dogs 2 and 3 dropped only slightly during the period of irradiation, while that of Dog 1 rose (perhaps compensatorily) during the first 3 days of the period of irradiation, but fell below the base line during the remainder of the period. During the post-irradiation period, the former levels were reached. The trend of Dog 4 dropped precipitously to a level nearly 50% below the base line during the period of irradiation followed by a compensatory rise after the period (see Graph I).

The hemoglobin, red blood cell and platelet levels varied insignificantly. In Dog 3 there was a marked decrease in the percentage of circulating eosinophils at the end of the pre-irradiation period.



GRAPH I.—The trends of the absolute numbers of circulating lymphocytes before, during and after dermal (Dogs II and III) and enteral (Dogs I and IV) irradiation.

Upon removing the capsules from Dogs 2 and 3 a distinct erythematous area, a "beta-radiation burn" (1.5 by 4 cm.—the size of the capsule) was observed. The lesions developed typical scabs. In 6 weeks the lesions were completely healed, without contracting scars and without the return of growth of hair.

Dogs 1 and 4 started to excrete pencil-shaped stools 2 days before the cessation of feeding the capsules. It was assumed that the capsules remained in the rectum for the longest periods of time and that edema of the rectal mucosa probably occurred. Both dogs excreted normal stools 1 week after the feeding of capsules was discontinued.

Discussion. It is obvious that the capsules given orally did not remain in the center of the lumen of the entire length of the intestinal tract, and that they moved more rapidly in the small than in the large bowel. These features, in addition to the fact that the greatest amount of ionization occurs just before the termination of the beta-ray, suggest that some portions of the submucosa received more ionization than the overlying mucosa. Since the amount of radiation was sufficient to kill hair follicles of the skin it can be assumed that destructive beta-radiation reached some of the germinal lymphoid follicles of the submucosa of the gastro-intestinal tract. Evidence has been presented to indicate that the majority of lymphocytes originate in these follicles¹ and that these follicles are quite frequently hyperplastic in patients with lymphoid leukemia,⁵ but less frequently involved in myeloid³ leukemia.² The marked variations in the absolute numbers of lymphocytes of Dogs 1 and 4 might be attributed to the effects of radiation upon these follicles.

Although the results are not conclusive, the experiment indicates another approach to the study of the origin of lymphocytes and indicates that enteral administration of radiation to human beings seems possible.

Conclusions. Beta-radiation, emitted by radio-phosphorus in the quantities and by the method described, applied dermally, was followed by slight anticipated changes (including a decrease in the absolute numbers of lymphocytes) in the blood levels of dogs; applied enterally it was followed by similar changes associated with significant variations of the absolute numbers of lymphocytes.

I wish to thank the members of the Crocker Radiation Laboratory and the Department of Physiology for materials and friendly cooperation.

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A DEFECT IN CLOT FORMATION OBSERVED IN THREE CASES OF CHRONIC AGNOGENIC HEMORRHAGIC DISEASE.*

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It is apparent that until more is known of the multiple mechanisms which prevent and arrest bleeding there will be no rational explanation for the many forms of abnormal hemorrhage. However, it is generally conceded that it is reasonable to expect prolonged bleeding times in patients displaying: 1, prolonged coagulation times in shed blood; 2, thrombocytopenia; 3, prothrombinopenia or fibrinogenopenia; 4, inflammatory, allergic, or metabolic disease affecting the integrity of vessels; and 5, leukemias and similar diseases which profoundly alter the constituents of the circulating blood. There remains a group of cases in which the prolonged bleeding time cannot be explained by exploration of all factors known to be concerned in hemorrhage. The majority of the recorded cases of prolonged bleeding time of unknown cause has not been fully investigated in the light of our more recently acquired knowledge of the pathology of coagulation. This paper discusses a possible mechanism for the prolonged bleeding time in 3 patients with abnormal hemorrhage of unknown etiology.

Case Reports. CASE 1.—*Hemorrhagic Diathesis, Acquired, Cause Unknown.* J. D. K., aged 27, male, mechanical engineer, was admitted to the University of Chicago Clinics September 14, 1940.

History: Abnormal bleeding commenced in 1935 at the age of 22 and has persisted ever since. Minor traumata contracted at games result in large subcutaneous effusions, and consequently much of the habitual athletic exercise has been abandoned. At the same time spontaneous epistaxis appeared, and at times has been more or less continuous. In 1937 gum hemorrhages due to gingival trauma became considerable and have continued intermittently.

Previous health: Scarlet fever, measles, whooping cough, and chickenpox before the age of 10; pneumonia at 7; tonsillectomy at 8 without excessive hemorrhage. Patient has always led the life of a healthy male.

Social: From 1932 to 1936 the patient, working his way through school, consumed a restricted dietary due to financial stringencies. In 1936 he weighed 135 pounds. He had increased to the present weight of 165 pounds by 1938. The present dietary is satisfactory and includes a plentiful fruit and vegetable intake.

Family: *There is no family history of abnormal hemorrhage.*

Four siblings are alive and well; 2 died at birth of unknown cause.

Physical findings: Patient is robust, the only abnormal physical findings are limited to evidences of old and new hemorrhages.

* Aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

Laboratory findings: Red blood cells, 4,830,000; white blood cells, 5300; hemoglobin, 16 gm. per 100 cc.; reticulocytes, 0.4%; polymorphonuclears, 70%; large lymphocytes, 3%; small lymphocytes, 15%; monocytes, 9%; eosinophils, 3%.

Bleeding Time: Repeatedly more than 30 minutes (Duke's method).

Coagulation Time (Wright's capillary tubes): Three minutes; 3 minutes and 25 seconds; 2 minutes and 55 seconds. (Howells' paraffin-coated test tube method): (1) patient, 20 minutes; control, 22 minutes and 50 seconds. (2) Patient, 18 minutes; control, 19 minutes and 50 seconds.

Platelet Counts (direct citrate technique of Todd and Sanford): Counts at various times ranged from 150,000 to 233,000 (normal).

Clot Retraction: Normal in time and completeness as compared with normal control.

Blood Fibrinogen: 0.31 gm. per 100 cc.; 0.30 gm. per 100 cc.

Fasting Blood Ascorbic Acid: 0.9 mg. per 100 cc. (normal).

Blood Calcium: 9.6 gm. per 100 cc.; 9.4 gm. per 100 cc.

Blood Prothrombin (dilution method of Allen, Julian, and Dragstedt): Repeatedly 100% of normal.

Capillary Fragility (quantitative, by suction method): Much in excess of normal. Not influenced by therapeutic vitamin K, ascorbic acid, "citric," or nicotinic acid.

Hepatic function tests, blood protein levels, Wassermann reaction, Kahn reaction, blood phosphatase, urinalysis, and sternal puncture findings were all within normal limits.

DISCUSSION OF CASE 1. It is observed that with the exception of the prolonged bleeding time and the excessive capillary fragility all findings were within normal limits. There is no evidence to exclude the possible contribution of a vascular factor to the abnormal hemorrhage in this case. There is no evidence which evaluates the relationship of the excessive capillary fragility with the abnormal properties of the patient's clotting mechanism as described below. *This situation is similar to that in thrombocytopenic purpura.*

CASE 2.—Hemorrhagic Diathesis, Probably Congenital, Cause Unknown. R. R., aged 30, female, housewife, was admitted to the University of Chicago Clinics February 15, 1940.

History: As a very young child the patient was known to bleed excessively from minor wounds, and also to bruise easily so that there was a family interdictment against spanking. Menstruation commenced at 16 years and has been extremely irregular from the first, and usually marked by a very heavy loss persisting up to 14 days. At the age of 21 years spontaneous epistaxes commenced and have increased in frequency. At 25 years, following an extraction, a tooth socket bled for 3 days. A small pericorneal hemorrhage occurred in the left eye at 28 years. Spontaneous subcutaneous hemorrhages have been increasingly frequent in the lower limbs during the past 2 years. More recently there have been symptoms and signs of increasing anemia.

Diet: Always satisfactory and includes plentiful fresh fruits and vegetables.

Family: *There is no family history of abnormal hemorrhage.*

Mother, father, and 5 sisters alive and well.

Physical findings: The patient is a small fragile individual who has recently become obese. The skull is large and boxlike with frontal bosses as in rickets (there are no signs of old rickets). The limbs show numerous

subcutaneous hemorrhages in every stage of resorption, and there is considerable pigmentation of the shins due to old hemorrhages. Signs of anemia are moderate edema of the ankles, pallor, tachycardia with signs of cardiac dilatation, and moderate dyspnea without exertion. Lungs, abdominal organs, and central nervous system are normal, as are also the genitalia.

Progress: This patient has been followed for a year, and displayed varying grades of hypochromic anemia dependent on the degree of menorrhagia. Hysterectomy or sterilization was refused. The essential bleeding phenomena have remained unchanged and uninfluenced by oral and intravenous ascorbic acid, testosterone, Roentgen rays to the spleen, and intravenous oxalic acid.

Laboratory findings: Red blood cells (on admission), 1,290,000; white blood cells, 7700; hemoglobin, 2 gm. per 100 cc.; polymorphonuclears, 81%; large lymphocytes, 1%; small lymphocytes, 17%; eosinophils, 1%.

Bleeding Time (Duke's method): Repeatedly more than 30 minutes and has remained at this level throughout the year.

Coagulation Time (Wright's capillary tubes): 3 minutes, 20 seconds; 2 minutes, 5 seconds; 2 minutes, 55 seconds. (Howell's paraffin-coated test tube method): patient, 17 minutes; control, 22 minutes, 25 seconds.

Platelet Counts (direct citrate technique of Todd and Sanford): 120,000 to 250,000.

Clot Retraction: Normal in time and completeness by comparison with normal control.

Blood Fibrinogen: 0.24 (on admission); 0.36 gm. per 100 cc.; 0.35 gm. per 100 cc.

Blood Calcium: 8.8 mg. per 100 cc. (on admission); 9.6 mg. per 100 cc.

Blood Ascorbic Acid: Not studied. Oral and intravenous ascorbic acid did not affect syndrome.

Blood Prothrombin (technique, of Allen, Julian, and Dragstedt¹): On admission, 37% of normal. Subsequent to administration of 2 mg. daily of 2-methyl-1, 4-naphthoquinone the prothrombin level returned to 100% of normal and has remained thereat throughout the year.

Capillary Fragility: Rumpel-Leede tests invariably strongly positive.

Non-protein nitrogen, urinalysis, Wassermann and Kahn reactions and serum protein levels were normal.

DISCUSSION OF CASE 2. If the abnormal bleeding tendency in this patient is not congenital, it was acquired at a very early age. At the time of first admission menorrhagic blood losses had conditioned a severe hypochromic anemia. Hypoprothrombinemia, discovered at first admission, responded well to therapy and has not recurred, but remains unexplained unless on the basis of the chronic blood loss. It did not apparently cause the hemorrhagic syndrome. The increased capillary fragility observed bears the same relationship to the consideration of the cause of the abnormal bleeding as that in the first case.

CASE 3.—Hemorrhagic Diathesis, Congenital, Familial, Cause Unknown. L. T., an 18-year-old schoolgirl, was admitted to the University of Chicago Clinics, March 11, 1930, and first studied by us in 1940, aged 28.

History: This patient has suffered subcutaneous hemorrhages over the body all her life. She first bled profusely at the age of 11 years after operation for tuberculous osteomyelitis of the left lower limb, and was then transfused several times. Menstruation, established at 15 years, was regular but profuse and lasted 7 to 10 days. Early tooth extractions had led to severe hemorrhages and the patient came to hospital for further dental

extractions on account of severe caries (1930). At this time the bleeding time was greatly prolonged, and the clotting time gave figures interpretable as slightly prolonged (in years subsequent to 1930 the clotting time by the Wright's tubes technique has invariably been within normal limits). The platelet count was then between 150,000 and 175,000 (direct citrate technique). At this hospitalization (1930) dental extractions were followed by hemorrhage and multiple transfusions. At the age of 21 a Cesarean section was shortly followed by hysterectomy and right oöphorectomy, many transfusions being necessary. At 26 years the patient was again hospitalized (1938) for dental extractions, again with troublesome hemorrhage. At 27 (1939) multiple transfusions were given for hypochromic anemia of unknown cause (possibly in part nutritional owing to a bad financial situation at this time; a marked ascorbic acid unsaturation was demonstrated, but the administration of ascorbic acid did not in any way affect the syndrome).

Family: Paternal grandfather, paternal uncle, and one brother have died of hemorrhage; father and one sister are known as bleeders. Son (aged 7 years) does not bleed abnormally.

Physical examination: The patient is of markedly asthenic habitus. Physical examination reveals the scars of operations, but is otherwise negative.

Laboratory findings: Red blood cells—throughout the past 10 years there have been varying degrees of hypochromic anemia usually conditioned by the immediate bleeding episode; white blood cells, altered only by immediate episodes.

Bleeding Time (Duke's method): Constantly over 30 minutes.

Coagulation Time: Except for dubious figures in 1930, always within normal limits (Wright's tubes); Howell's paraffin-coated test tube method (1940): patient, 20 minutes 25 seconds; control, 20 minutes 0 seconds.

Platelet Counts, 1940 (direct citrate technique): 210,000 to 235,000.

Clot Retraction, 1940: Normal by comparison with normal control.

Blood Fibrinogen: 0.17 gm. per 100 cc.; 0.27 gm. per 100 cc.

Blood Calcium: 9.3 mg. per 100 cc.; 9.4 mg. per 100 cc.

Blood Ascorbic Acid: Patient was found defective in ascorbic saturation in 1939, but oral and intravenous ascorbic acid did not affect the bleeding time.

Prothrombin Time: 100% of normal (dilution technique).

Capillary Fragility: Moderately increased by suction technique. Rumpel-Leede test gives moderate number of petechiae.

DISCUSSION OF CASE 3. The family history displays three generations of hemorrhagic disease which has included both sexes. This case must therefore be assigned to the group of so-called "atypical familial hemorrhagic syndromes" (Geiger and Evans³) or "hereditary pseudo-hemophilias" (Fowler²). Some of these familial syndromes resemble thromboeytopenia, while others simulate hemophilia in that coagulation time is prolonged. But most commonly bleeding time is prolonged with normal coagulation time (v. Glanzmann's syndrome, v. Willebrandt's syndrome, etc.), and it is apparently to this group that our patient belongs. It is not desirable here to discuss these syndromes at any length. Reference should be made to the papers of Fowler,² and of Geiger and Evans.³ Again, it is pointed out here that we have no evidence to exclude the participation of a vascular factor in the causation of the abnormal hemorrhage.

The Thromboplastin Dilution Curve. Technique: The patient's and the control's blood were withdrawn at the same time into one-seventh volume of 1.85% potassium oxalate in paraffined containers, and both samples centrifuged approximately 1 hour at 2000 revolutions per minute at room temperature. The supernatant plasma was pipetted into small, uncoated tubes at room temperature and coagulation observations made as soon as possible. *Although delay up to 12 hours between the separation of the plasmas and the observation of their coagulation properties lengthened the coagulation times of both patient's and control's plasmas, it did not affect the peculiar relationship as to time and clot characteristics reported below.*

Thromboplastin dilution curves were obtained by timing the coagulation of patient and control essentially as in the prothrombin time technique* (Allen, Julian and Dragstedt¹), but employing progressive dilutions of the stock beef lung thromboplastin.

The necessity of handling control and patient's bloods simultaneously and in identical fashion is emphasized.

TABLE 1.—TIME OF CLOT FORMATION IN MINUTES.

Thromboplastin Dilutions.	Case 1.		Case 2.		Case 3.	
	Patient.	Control.	Patient.	Control.	Patient.	Control.
1-4 . . .	0.70	0.67	0.57	0.59	0.62	0.64
1-16 . . .	0.90	0.94	0.82	0.88	0.79	0.84
1-64 . . .	1.44	1.38	1.25	1.20	1.23	1.42
1-256 . . .	2.44	2.28	2.22	1.88	2.01	2.07
1-1024 . . .	4.20	3.51†	4.70*	2.70	3.70	3.32
1-4096 . . .	10.60*	5.92	5.80*	3.57	4.90*	4.20
1-16,384 . . .	8.60*	5.55	5.70*	5.90
1-infinity . . .	12.33*	6.95	11.40*	6.18	7.45*	6.20

Discussion. The table presented is taken as representative of at least 4 observations in each case at different times. In all 3 the quantitative difference in clot size and retractability (see photographs) were constantly present at high thromboplastin dilutions. In Case 1 the time difference of clot appearance at high dilutions was constantly in excess of that of the controls. In Case 2 the time difference was never as marked, and was indeed not constantly present to a degree regarded as significant; but nevertheless at high dilutions of thromboplastin the time of clot appearance was always in excess of that of controls. In Case 3 at no time was there a significant difference in the time of clot appearance. However, in all 3 cases the quantitative difference in clot size and retractability was striking. At high thromboplastin dilutions, and also in the tubes to which no extra thromboplastin was added, the controls

* To 0.35 cc. plasma is added 0.30 cc. of the given thromboplastin dilution in saline, and time is reckoned from the moment of recalcification with 0.30 cc. of 0.5% calcium chloride in saline to the moment of formation of the fibrin network.

† Clots formed at these dilutions showed quantitative and qualitative differences from the controls as described.

(J. G. A. or G. C.) displayed invariably clots of large size which formed completely in the sense that there was no further subsequent demonstrable deposit of fibrin. Such clots underwent only moderate contraction. By contrast, at these dilutions, the patient's clots

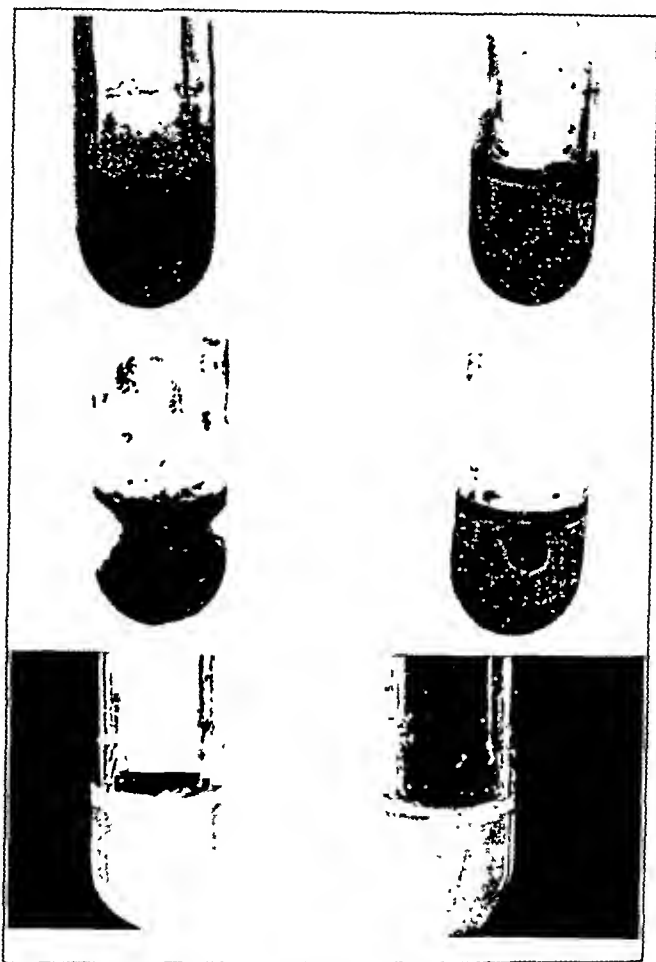


FIG. 1.—Photographs show the clots resulting on the addition of 0.3 cc. of 0.5% calcium chloride and 0.3 cc. of diluted thromboplastin to 0.35 cc. of oxalated plasma. In each case the control is on the left and patient's plasma on the right.

Case 1: Thromboplastin diluted to 1:1024.

Case 2: Thromboplastin diluted to 1:4096.

Case 3: No added thromboplastin, samples brought up to volume with saline.

consisted of tenuous threads which very rapidly contracted into a small firm mass of fibrin, and some time thereafter the remaining fluid formed a transparent, non-retractile gel. We would have no confidence in these differences were they not constant and striking.

The thromboplastin dilution curve here is the function of two

factors: the natural thromboplastin resulting from the breakdown of the cellular elements accompanying the withdrawal and handling of the blood samples, and the thromboplastin contained in the added lung extract. The clotting time of plasma containing an infinitely small amount of added thromboplastin is, of course, representative of the recalcified plasma time, whereas the clotting time recorded in tubes with considerable excess of thromboplastin is essentially prothrombin time. The dilution curve then is simply the gradient record encountered in the transition from the prothrombin time to the clotting time of recalcified plasma.

The mechanism responsible for the differences of coagulation observed by this technique might be explained on one of three considerations: (1) an Inhibitor contained in the patient's plasma might exert its influence on coagulation only when the thromboplastin activity is weak. (2) There might exist in the patient an abnormal relationship between fibrinogen and thromboplastin, made manifest only when the latter is very dilute. (3) The differences in the plasma responses might depend on the different concentrations of natural thromboplastin contained in the samples. We have been unable to adduce any evidence which points to the unqualified acceptance of any of these three possibilities, and in fact there is none to support the first two. In view of the normal prothrombin time, the normal coagulation time, and the disappearance of these clot differences when the samples are coarsely handled in wettable surfaces it would appear to be most logical to believe that the variations depend on the different concentrations of natural thromboplastin in patient's and control's samples.

Moreover, it appears significant to us that at some point along the thromboplastin dilution curve the thromboplastin concentration must approach that present in the wound produced in the observation of bleeding time. It is possible that the observed clot differences at high dilutions of thromboplastin *in vitro* may offer an explanation of the prolonged bleeding time characteristic of these patients.

It has long been recognized that the thromboplastic substances liberated by shed blood are in considerable excess of that required for normal coagulation. It is to be expected, then, that *in vitro* coagulation of whole blood (coagulation time) will not demonstrate differences in clotting time when only a minor thromboplastin deficiency exists. Such variances from normal may only become manifest when the available thromboplastin is reduced below a critical level, such as in "cell free" plasma handled in unwettable surfaces. Likewise, the amount of additional thromboplastin necessary to restore the coagulation of the abnormal to that of the control is a measure of the deficit of natural thromboplastin in the test plasma.

These observations tend to reemphasize the importance of the study of the coagulation properties of recalcified plasma in the

investigation of hemorrhagic disease. It is to be noted, however, that we have observed a fourth case with prolonged bleeding time of unknown cause with history and findings identical with Case 1 (except that capillary fragility appears normal) in which no coagulation differences could be demonstrated by these techniques. It is possible that the demonstrated differences in the plasma of the 3 cases reported may contribute to the bleeding tendency. It is not known to what extent the demonstrated increase in capillary fragility may also condition the syndrome.*

Summary. 1. Three cases of chronic idiopathic hemorrhagic disease with prolonged bleeding time have been studied.

2. In each there has been demonstrated differences in the nature of the clots produced *in vitro* when recalcified plasma is allowed to coagulate.

3. The thromboplastin dilution curve points to deficiency in the natural thromboplastin content of the plasma as the source of these differences.

4. Such differences may contribute to the hemorrhagic tendency.

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IDIOPATHIC HYPOPROTHROMBINEMIA—AN APPARENTLY UNRECORDED CONDITION.

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THE unexpected finding of a prothrombin deficiency in a supposed hemophiliac led to a more detailed study of the defects of this patient's blood coagulability. The findings made it impossible to classify the case with any blood dyscrasia known to us.

Since the development of methods for determining plasma prothrombin by Quick,^{5a} by Warner, Brinkhous and Smith,¹² and by Dam and Glavind² and Schonheyder,⁸ there has been general agree-

* It is, moreover, to be pointed out that in the absence of an acceptable method of quantitative comparison of tissue thromboplastins it is not possible to present evidence which excludes variations in the tissue factor as contributory to the hemorrhagic syndrome. Inasmuch as our results were obtained on plasmas from large samples of blood removed by venipuncture, extravascular thromboplastic substances are not concerned with the coagulation differences demonstrated in this paper.

ment that there is no deficiency of prothrombin in hemophilia. This has been confirmed in our own laboratory also.

In the case of the patient to be reported, however, a marked prolongation of the prothrombin time was found shortly after the laboratory began to employ the Quick^{5b} test in 1938. The patient was then a 16-year-old boy who had been studied from the age of 6 during 15 previous admissions on the Pediatric and Medical Services of the Hospital of the University of Pennsylvania. The diagnosis had always been hemophilia.

Because of the hypoprothrombinemia it was necessary to abandon the diagnosis of hemophilia and that of idiopathic hypoprothrombinemia was substituted. In view of the early onset of symptoms, the condition may well have been congenital. The family history was negative and the plasma prothrombin concentration of the mother and brother whom we were able to test were normal. It was, therefore, impossible to classify the condition as familial. The case differed from the typical case of hemophilia in one other regard, namely that clot retraction was poor. The case history and the results of various laboratory studies are given in detail below.

Case History. E. W. (Med. rec., 35-21280), a white male, of Irish stock, born February 12, 1923, was first admitted to the University Hospital on November 9, 1929, on account of a tendency toward uncontrollable bleeding from wounds and development of large hematomas following contusions. At the time of admission he had a hematoma on the forehead which had been present for 6 weeks. His mother stated that the first such swelling occurred at the right knee at the age of 9 months. No aspiration was done but in view of his subsequent history it seems likely that this was a hemarthrosis. However, prior to his admission to the hospital he had been under the care of Dr. I. Kaplan, of Philadelphia, who reported that a cervical abscess had been drained without postoperative hemorrhage, but that on two other occasions incisions had resulted in serious bleeding, lasting 2 to 3 days and requiring transfusion to combat a decline in hemoglobin to 30%. Inquiry into the family history at the time of this first admission was negative for any abnormal hemorrhagic tendency. The patient's father was 40 years old, his mother 30 at the time of his birth, one aunt had died of tuberculosis 12 years previously and one uncle had had inflammatory rheumatism in 1927.

Past Medical History. The patient had been a full-term, 8-pound baby, delivered spontaneously; he appeared entirely normal as an infant. He was breast fed for 4 months and then given a formula until the age of 19 months. His early development was normal. He had pertussis at the age of 3 and measles at the age of 4.

Course in the Hospital. Study on the Pediatric Ward revealed a venous coagulation time of 41 minutes and a diagnosis of hemophilia was made.

Allergy to sheep serum was induced but the coagulation time remained 41 minutes when next determined. A blood transfusion of 265 cc. was given December 12, 1929; 6 days later the coagulation time was again found to be 41 minutes. The hematoma was absorbed and the patient discharged December 23, 1929.

Second Admission. December 2 to December 14, 1930. At this time he was treated for a hematoma in the region of the right ankle which came on following a blow. Blood was aspirated from the hematoma and was sterile on culture.

Third Admission. January 19 to January 25, 1931. For hemorrhage from the socket of a loose incisor, he received blood intramuscularly and also a transfusion, but the hemorrhage continued. It was finally controlled with silver nitrate stick, adrenalin and compression applied locally.

Fourth Admission. August 5 to October 25, 1931. A secondary hemorrhage from a laceration of the foot had been sustained 2 weeks before. At this admission he was treated with theelin but the coagulation time following this treatment was 50 minutes. An injection of liver extract for parenteral administration (Lederle) also failed to improve it.

Fifth Admission February 24 to March 23, 1932. For a hemarthrosis of the left hip he was given Armour's ovarian extract without definite improvement in blood coagulability.

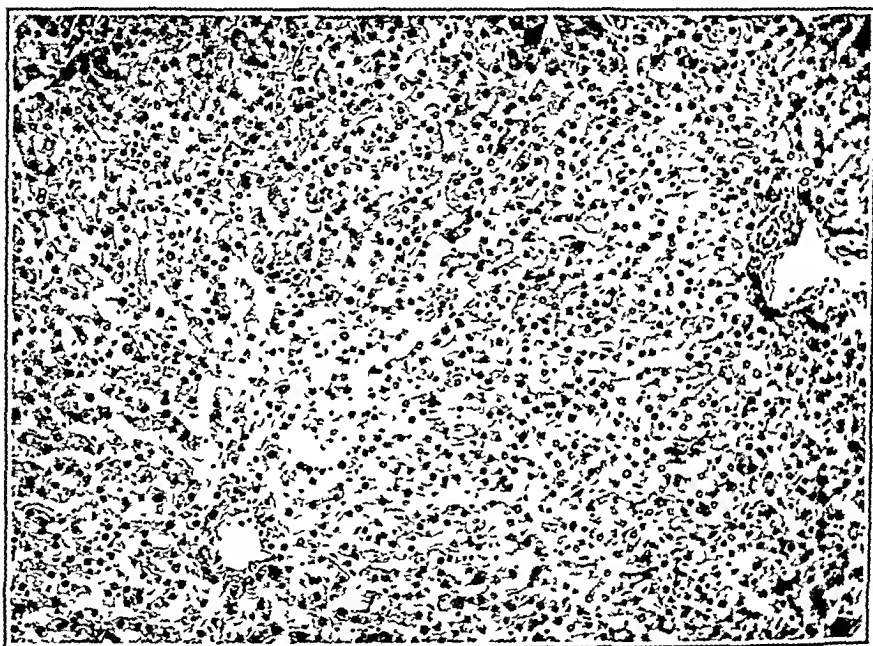


FIG 1 —Liver of E W obtained at autopsy ($\times 170$) The liver columns show considerable atrophy in many places. There is some slight cell vacuolization and the sinusoids are unusually large.

Sixth Admission August 5 to August 10, 1932. For hemorrhage from gums, which started 5 days before, a thromboplastin preparation was applied locally without success. On August 8, 17 cc of the patient's blood was drawn and injected into the buttocks. The bleeding stopped within 24 hours. Unfortunately, the coagulation time was not determined.

Seventh Admission. May 27 to June 13, 1933. The patient was admitted on a precautionary basis for extraction of carious teeth. This procedure was carried out successfully after a 300 cc. blood transfusion. He was given 20 cc of his own blood intramuscularly with the result that the puncture wound in the buttocks bled for several days.

Eighth Admission February 11 to February 26, 1934. For bleeding from cut on lip, a compress soaked with his mother's blood failed to stop the hemorrhage. Anterior pituitary hormone (1 cc.) was given intramuscularly; adrenalin was applied locally. Compresses of raw beef were

applied. Finally, 100 cc. of blood from a woman in the maternity department who was about to deliver a baby was administered. The oozing ceased about 1 hour afterwards.

Ninth Admission. July 23 to July 27, 1934. Bleeding from a cut on hand, which had persisted for 2 days, was stopped apparently by local measures; no new procedures were employed.

Tenth Admission. November 26 to November 28, 1934. This admission was also arranged for extraction of a tooth. The extraction was successfully accomplished after a 320 cc. transfusion from his mother. Glucose (50%) was applied on a compress.

Eleventh Admission. November 5 to November 23, 1935. Hemarthrosis of right elbow had occurred without history of trauma. During this admission intradermal horse serum was employed and a marked local reaction was produced but no improvement in the clotting time resulted. On November 20 he was given 10 cc. of Congo red intravenously. This also was without effect. Roentgen ray examination of the joints did not show bone changes.

Twelfth Admission. December 16 to December 24, 1935. This admission was arranged for observation and for a trial of placental extract. After 500 cc. was given by mouth, the coagulation time declined to 30 minutes.

Thirteenth Admission. February 3 to February 20, 1936. Hematoma of right thigh. The placental extract was given further trial but failed to produce any improvement.

Fourteenth Admission. March 9 to June 21, 1936. Swelling of right knee and left shoulder. During this admission he received crystalline vitamin C, 200 mg. per day for 1 week. This did not decrease the coagulation time. An electrocardiogram at this admission showed left axis deviation. Kahn and Kolmer tests for syphilis were negative. On June 17 and June 18 he was given a total of 180 r units of Roentgen ray over the spleen, kidneys and liver.

Fifteenth Admission. December 30, 1936, to January 4, 1937. Bleeding from mouth had been started by eating hard candy. It stopped spontaneously. His hemoglobin was 58%, so apparently he did not bleed a very large amount.

Sixteenth Admission. July 9 to August 6, 1937. Hemarthrosis of right knee following a fall. He received three 250 cc. transfusions of his mother's blood.

Seventeenth Admission. March 14 to June 3, 1938. Pain in thighs and bleeding from teeth. March 20, a tourniquet test was negative. During this admission a prothrombin determination was done for the first time. The prothrombin time ranged from 70 to 120 seconds, as compared with 20 to 24 seconds for the normal controls. Vitamin K was administered in the form of Cerophyl and the coagulation time dropped to 15 minutes at one determination, but soon returned to 90 minutes and did not drop to low levels again. The prothrombin time remained prolonged. The serum calcium during this admission was 9.8 mg. per 100 cc. The indirect Van den Bergh reaction gave a reading of 0.2 unit.

Eighteenth Admission. July 6 to August 3, 1938. Hemarthrosis left shoulder, which developed after rowing a boat. During this admission Dr. G. Ham made a preparation of human globulin according to directions received from Dr. L. Taylor (Thorndike Memorial Laboratory, Boston). The material corrected the coagulation time of the patient's blood *in vitro* but not *in vivo*.

Nineteenth Admission. October 11 to October 24, 1938. Bleeding from tooth socket for 6½ days. During this admission more of the specific globulin was administered. This caused a drop in the coagulation time to 20 minutes, but also caused rather a severe reaction with a chill and fever.

Twentieth Admission. December 7 to December 15, 1938. Bleeding from the mouth, which was controlled by the local application of thromboplastin. During this admission his clotting time was found to be 5 hours.

Twenty-first Admission. April 14 to April 20, 1939. Bloody urine, which subsided without specific treatment.

Twenty-second Admission. March 16 to March 30, 1940. The patient was admitted for study. The plasma fibrinogen concentration was found to be normal and a test for the presence of antithrombin was negative. A tourniquet test was positive (25 petechiæ). Studies of liver function (Dr. T. Machella): Van den Bergh plus or minus 0.2 unit, bromsulphthalein retention at 5 minutes 45%, at 30 minutes 0. Urine: urobilin 0, bilirubin 0, bile salts 0, hippuric acid conjugation 0.75 gm. per hour (normal 0.7 to 0.9). Glucose tolerance: fasting blood sugar 70 mg. per 100 cc.; $\frac{1}{2}$ hour 107 mg. per 100 cc.; 1 hour 122 mg. per 100 cc.; 2 hours 93 mg. per 100 cc. Cholesterol 164 mg. per 100 cc.; cholesterol esters 108 mg. per 100 cc. Ratio of esterified cholesterol to total cholesterol 66%. Urea clearance 135% of the average normal. The patient was given 9 mg. of 2-methyl, 4-amino, 1-naphthol hydrochloride by continuous venoclysis without affecting the prothrombin time.

Twenty-third Admission. August 28 to October 16, 1940. Hemarthrosis of left hip. On August 29 he had bleeding from the mouth and received a transfusion and Koagamin (extract of the Shepherd's purse). During this admission an adductor palsy developed with sensory changes referable to the second, third and fourth lumbar roots.

Twenty-fourth Admission. October 21 to November 2, 1940. Hematoma of left elbow.

Twenty-fifth Admission. November 9 to November 25, 1940. Recurrent hemarthrosis left elbow and hematuria. During this admission he received 5 cc. of Koagamin intravenously. Coagulation time before this medication was over 90 minutes; 20 minutes later it was still over 90 minutes and at the end of 2 hours it remained over 90 minutes. He received nicotinic acid during this admission.

Twenty-sixth Admission. December 3 to December 14, 1940. Hemarthrosis of the right elbow. On December 13 the patient complained of headache and it was noted that his neck was stiff. At 1 A.M. on December 15 he fell out of bed, became stuporous shortly afterward and died at 3.05 A.M.

Autopsy. Age 18, weight 42 kg. Heart, normal; lungs, passive congestion, edema and hemorrhage. Spleen, normal. Pancreas, normal. Liver, liver columns show considerable atrophy. There is some cell vacuolization and the sinusoids are unusually large. Adrenals, pericapsular hemorrhage. Kidney, submucosal hemorrhage in pelvis, passive congestion. Bladder, submucosal and subserosal hemorrhage. Ileum, serosal hemorrhage, granulomatous tissue in submucosal layer. Brain, organizing subdural hematoma and a recent hemorrhage in the region of the left basal ganglia. This hemorrhage was thought to be the immediate cause of death.

Hematologic Studies. The studies of the coagulability of the patient's blood are summarized in the accompanying tables. The bleeding time was sometimes prolonged and sometimes within normal limits. The venous coagulation time by the Lee-White method was always prolonged, except on two occasions and because it was not checked at these times it is doubtful if they are significant. The clot retraction was regarded as normal at two of the earlier examinations, August 6, 1931 and March 14, 1932. It was retarded

February 16, 1934, and was noted as poor October 18, 1938 and March 18, 1940. The platelet count was usually normal and was never low enough to account for the hemorrhagic diathesis. The serum calcium concentration was determined twice, on May 2, 1938, it was 9.8 mg. per 100 cc.; on March 18, 1940, it was 10 mg.

TABLE 1.—BLEEDING TIME (DUKE METHOD).

Dates.	Times (min.).	Dates	Times (min.).
11/ 9/29	2	11/18/35	1½
12/ 4/30	2	2/10/36	1
8/ 6/31	20	6/21/36	2
2/25/32	25	3/18/40	1½
5/27/32	22	8/28/40	9
2/16/34	1	11/11/40	6
7/23/34	4	12/ 4/40	10

TABLE 2.—VENOUS COAGULATION TIME (LEE, WHITE METHOD).

Dates.	Times (min.).	Dates.	Times (min.).
11/ 9/29	41	10/25/34	70
12/ 4/30	46	11/22/34	90
10/30/31	65	11/18/35	90
8/ 6/31	43	2/10/36	120
3/14/32	27	6/21/36	48
5/27/33	15	9/28/38	45
2/16/34	58	10/18/38	200
7/23/34	30	3/18/40	75
8/10/34	38	8/28/40	105
8/24/34	8	10/21/40	360
9/12/34	57	11/11/40	35
10/ 7/34	75	12/ 5/40	45

TABLE 3.—PLATELET COUNTS.

Dates.	Thousands per c.mm	Dates.	Thousands per c mm
11/ 9/29	276	5/29/33	350
11/12/29	302	2/26/34	384
12/ 4/30	288	5/21/36	281
1/24/31	140	2/25/38	230
10/ 7/31	345	3/18/40	326
2/25/32	416	8/29/40	148

TABLE 4.—PROTHROMBIN TIME.

Dates.	Times (sec.).	Dates.	Times (sec.).
3/30/38	90	11/ 6/39	100
4/ 3/38	90	5/15/40	93
4/ 7/38	85	9/12/40	107
4/ 9/38	70		

per 100 cc. The prothrombin time by the Quick method was uniformly prolonged (Table 4). The fibrinogen concentration, March 26, 1940, was 315 mg. per 100 cc. The following test was performed for antithrombin: The patient's plasma was mixed with the plasma of a normal patient in equal parts. The prothrombin time of the plasma of the normal patient was 23 seconds. The prothrombin time

of the mixture was 27 seconds. This is the usual prolongation obtained by diluting normal plasma with prothrombin-free fluid and was not thought to indicate that the plasma of E. W. had any excess of antithrombin or antiprothrombin.

A solution of protamine (Salmine) was added to the patient's plasma to see if an excess of heparin was causing the delayed clotting. This was without effect, a finding which agrees with the results of the test for antithrombin referred to above.

In order to exclude the possibility that the prolonged prothrombin time was due to a delay in the conversion of prothrombin to thrombin, the following test was carried out: Fresh normal serum was added to the patient's plasma to convert the fibrinogen to fibrin. This fibrin was then removed and the patient's plasma recalcified, after the addition of thromboplastin. In 60 seconds a solution of fibrinogen was added and a clot formed 48 seconds later. The dilution of the patient's plasma was only 2 to 1. This determination, carried out along the lines recommended by Smith, Warner and Brinkhous¹² tended to confirm the fact that the prothrombin content was quantitatively low and not merely at fault qualitatively. When the same procedure was repeated using a 2-minute incubation period before the addition of fibrinogen, a clot formed at the end of 110 seconds, indicating that the thrombin which had been added previously had not completely removed the fibrinogen in the original sample of plasma. This is of interest because it had been noted in the course of the fibrinogen determinations that it seemed to take a long time to get all of the fibrinogen converted to fibrin. Accordingly it seemed worthwhile to test the influence of the addition of fibrinogen preparations from normal blood and of prothrombin-free plasma, prepared from normal blood with the aid of colloidal aluminum hydroxide. On November 6, 1939, the addition of a fibrinogen solution reduced the prothrombin time from 100 to 80 seconds. In May, 1940, the addition of fibrinogen solution reduced the prothrombin time from 93 to 49 seconds. This fibrinogen solution was tested for the presence of prothrombin by the Quick test and there was no clot formation at the end of 600 seconds. A prothrombin-free plasma was prepared by shaking 10 parts of normal plasma with 1 part of colloidal aluminum hydroxide for 5 minutes. The aluminum was separated by centrifugation at high speed and the resulting plasma was free of prothrombin by the Quick test,^{5b} no clot formation being observed at the end of 600 seconds. A mixture of equal parts of this plasma with the plasma of E. W. gave a prothrombin time of 41 seconds, as compared with 93 seconds for E. W.'s plasma undiluted, and as compared with 49 seconds for a mixture of equal parts of E. W.'s plasma and fibrinogen solution. These figures compare with the normal prothrombin time of 23 seconds. It would seem, therefore, that the

coagulation defect in this case was due partially to a peculiarity or qualitative defect, in the fibrinogen. This was further borne out by the observation that the addition of fresh normal serum to the plasma of E. W. produced a sediment in 30 seconds but no firm clot for 2 minutes. A prothrombin time of 93 seconds, as compared with the normal 23 seconds, would indicate a plasma prothrombin concentration in the neighborhood of 10%. Dilution of the patient's plasma with equal parts of saline, however, only prolonged the prothrombin time from 93 to 126 seconds, which would suggest that the actual prothrombin content was not quite this low.

Discussion. Over ten methods are now available for the production of hypoprothrombinemia in various species.⁷ There are, however, only five mechanisms by which these methods work. The first is simple K-avitaminosis, as employed in the chick by Dam, Almquist and others. The second is a conditioned deficiency for vitamin K, produced by a lack of bile salts required for its absorption from the intestinal tract, as in the dogs with internal biliary fistula, reported by Hawkins and Whipple,⁴ and Hawkins and Brinkhous.³ This is the mechanism commonly operative in the hemorrhagic tendency of obstructive jaundice. The third is hepatic damage. This has been observed in the experimental animal following chemical and mechanical trauma to the liver and following surgical ablation of the liver. It has been found also in patients with prolonged common duct obstruction and certain other disorders. The fourth method is that observed in sweet clover disease,^{5c} in which a toxic material developing in spoiled clover hay¹⁰ is absorbed and reduces the plasma prothrombin concentration without gross liver damage. Fifth, certain cases of clinical hypoprothrombinemia have been attributed to changes in the intestinal tract interfering with absorption of the vitamin, as in sprue and ulcerative colitis.¹ The question arose as to which of these mechanisms, if any, could have been operative in this patient. Simple K-avitaminosis responds rapidly to the administration of small amounts of vitamin K. In 1938 E. W. received Cerophyl 7.5 gm. per day with bile salts 2 gm. per day for a period of a week without any response. In 1939 he received 2-methyl-1, 4-naphthoquinone mg. (various amounts) t.i.d. over a week with the same dose of bile salts with no improvement. In 1940 he received 2-methyl, 4-amino, 1-naphthol hydrochloride 9 mg., by continuous intravenous infusion in 24 hours with no response. It would seem, therefore, that he did not suffer from K-avitaminosis nor from a conditioned deficiency of vitamin K, due to a lack of bile salts.

It is well known that hypoprothrombinemia due to liver damage is not very responsive to treatment with vitamin K, either by oral or parenteral routes. It seemed most likely, therefore, that this patient had hepatic damage or perhaps hepatic hypoplasia, such as

was found in a patient with congenital hypoproteinemia, described by Thompson, McQuarrie and Bell.¹¹ None of the liver function tests showed any evidence of hepatic damage. At autopsy no gross abnormality of the liver was discernible, and the microscopic changes were much less than we have observed before in patients with hypoprothrombinemia due to liver damage (Fig. 1).

The possibility of a toxic agent which destroyed prothrombin directly seems unlikely as the patient showed no improvement with changes in diet and environment. There were no symptoms pointing to a disorder of the digestive tract and as the patient did not respond to vitamin K administered parenterally, it would seem that the hypoprothrombinemia could not be due to a failure to absorb vitamin K in this case. The possibilities of an excessively low threshold for vitamin K excretion, resulting in a prompt loss of vitamin K, was considered and an antivitamin K factor immediately destructive of all but a small part of the vitamin K received was also considered. Neither of these conditions has been recognized previously and it was felt that the continuous administration of 2-methyl, 4-amino, 1-naphthol hydrochloride by vein for 24 hours in excessive dosage would have yielded a measurable response in the face of either of these possibilities. The studies carried out in this patient indicate that his coagulation defect was due to a lack of prothrombin and to a qualitative defect in fibrinogen without a quantitative defect in this factor. It should always be remembered in discussing prothrombin that this factor is known only by its function. It has never been isolated or measured quantitatively. There is no certain evidence to indicate whether it is a single substance, a group of substances, or a complex of factors which interact chemically to achieve the function which we measure.

Conclusions. The case of an 18-year-old, white male with a hemorrhagic diathesis extending over most of his life span is presented. The defect appeared to be due to an idiopathic hypoprothrombinemia and an abnormality of the fibrinogen which was evidenced by an unusual resistance to the action of thrombin. We have been unable to classify this case with any of the known hemorrhagic diatheses.

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INTRAVENTRICULAR BLOCK, INCLUDING SO-CALLED
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THE diagnosis of intraventricular block is entirely dependent upon the electrocardiogram and has as its cardinal sign a *QRS* duration of 0.12 second or longer. Two major varieties have long been recognized on the basis of the contour in the limb, viz., the common type with *QRS*₁ upright and *QRS*₃ inverted, and the uncommon type with *QRS*₁ inverted and *QRS*₃ upright. Earlier workers^{16,33,48} interpreted the common type as due to delay of stimulation in the right ventricle and the uncommon type as due to delay in the left. This was the accepted interpretation with only occasional dissent^{18,35,43,44} until Barker, Macleod and Alexander⁵ in studies on the exposed human heart presented evidence that extrasystoles with *QRS*₁ upright were from the right ventricle and that extrasystoles with *QRS*₁ inverted were from the left ventricle. Wilson and his coworkers⁶¹ demonstrated that the common type of bundle block was associated with block of the left bundle branch and the uncommon with block of the right. They^{59,60} supported their experimental work by studies of chest leads on dogs and man. In this latter work the interpretation was based upon the relatively early or late rise of the so-called "intrinsic deflection" in leads over the various parts of the chest; but this interpretation of the deflection may be subject to criticism. Later experimental work^{1,2,31a,b,32,37,47,55} has tended to confirm the broad principles of Wilson's view.

There are, however, instances in which a prolonged *QRS* interval is present but in which the contour of the curves do not fit into either of these two classical patterns. For lack of a better term these have been designated as "indeterminate" types. Necropsy reports^{14,17,24,26,34a,b,43,44} have been more or less inadequate for correlation with the electrocardiogram and have often been rather confusing. The recent detailed work of Yater^{66,67} indicates that

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branches of both bundles are often affected at the same time, especially in arteriosclerotic heart disease. This may in part at least account for the atypical forms of some of the electrocardiograms. The variations in the contour of chest leads associated with these different types of intraventricular block have been described,^{12,27,37,39,40,46,59,60,63,65} but there is still considerable confusion as to the significance of these variations. On this account, we have undertaken a more detailed study of the chest lead deviations occurring with the different limb lead electrocardiographic pattern in order to see if such an analysis may be helpful in evaluating the extent and nature of the involvement of the conducting system of the ventricles.

Material Employed. A total of 176 cases were studied and 1245 curves were analyzed and classified. In 12 cases, leads were taken with the chest electrode at various positions encircling the chest at the level of the second and fourth intercostal space at the sternal margin. The technique used was similar to that in our previous report.¹⁰ In 44 others, 6 leads from the anterior chest were used (with the left leg the "indifferent" electrode). These were: 1, at the right of the sternum at the level of the fourth intercostal space; 2, at the left of the sternum at this level; 3, at the left midaxillary line at this level; 4, at the apex; 5, over the mid-sternum at the level of the second intercostal space; and 6, over the junction of the xyphoid and sternum. Besides these, 30 other cases are included in which the standard 5 leads used by us at present were recorded, the chest leads being CF_2 and CF_4 .⁵³ In addition, 91 further cases were also included in which standard 4 leads previously employed by us were recorded, the chest lead being CF_2 . In 43 of the 176 cases the subclavian arterial pulse was recorded simultaneously with Lead II to determine the Q - E interval.²⁹ In 25 cases autopsy reports were available.

Analysis of Material. 1. DISTRIBUTION. (a) *By Type.* The electrocardiograms of the 176 individuals were classified into four types illustrated in Figure 1. For clarity these four groups are defined more precisely as follows:

1. The *common type* in which QRS_1 is upright and of the Λ or μ type (with the first inverted phase tiny) and T_1 is inverted or diphasic, while QRS_2 is usually inverted and of the V or N type (but may be upright) and T_2 is usually upright (but may be inverted).

2. The *first indeterminate type* in which QRS_1 is upright of the N or W type and T_1 is inverted or diphasic. It differs from the common type in having a small final inverted phase. QRS_2 is usually inverted and of the N or M type and T_2 is upright. This is like the type classified by the New York Heart Association,⁴² under right bundle branch block (see Fig. 20*b* of Nomenclature for Diagnosis of Diseases of the Heart).

3. The *second indeterminate type* in which QRS_1 is diphasic and

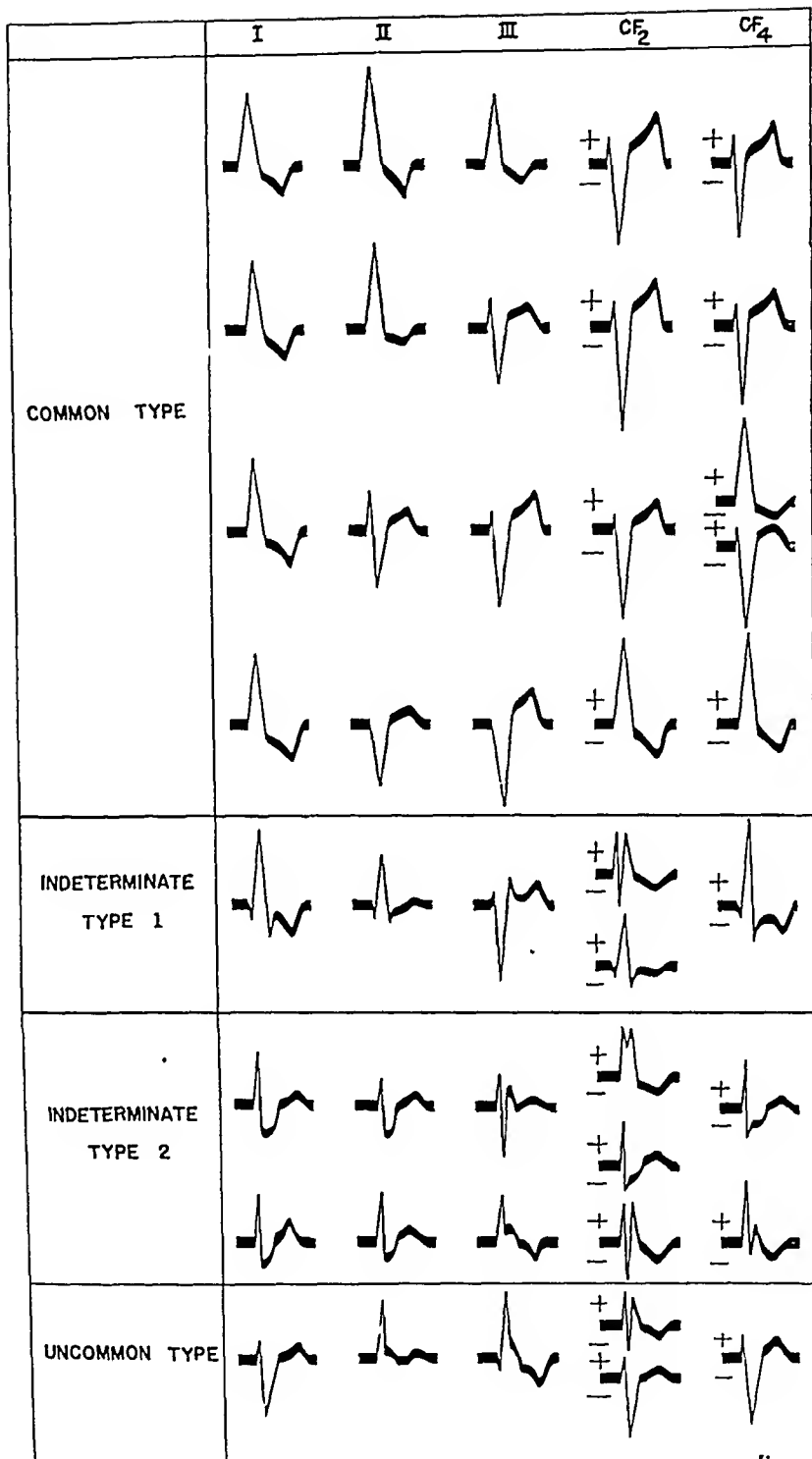


FIG. 1.—Chart Showing the Chief Varieties of Contour of the *QRST* in the 4 Types of intraventricular block in Leads I, II, III, CF₂ and CF₄.

In CF₂ and CF₄, relative positivity and negativity of the chest electrode with respect to the leg electrode is shown by + and -. Discussed in text.

There were 10 cases like the 1st line, 33 cases like the 2nd line, 34 cases like the 3rd line, 12 cases like the 4th line, making a total of 89 (51%) of the common type. There were 23 cases (13%) of the first indeterminate type like the 5th line. There were 17 cases like the 6th line and 42 cases like the 7th line, making a total of 59 (33%) of the second indeterminate type. There were 5 cases (3%) of the uncommon type like the 8th line.

The average *QRS* duration in the series was 0.135 sec. and the range 0.12 sec. to 0.24 sec.

of the N type with a deep prolonged S_1 ; T_1 is usually upright. It differs from the uncommon type in having QRS_1 diphasic instead of mainly inverted.

4. The *uncommon type* in which QRS_1 is inverted or mainly inverted and of the N, or rarely V, type; usually there is a deep S_1 and T_1 is upright. QRS_3 is upright and T_3 is usually inverted.

Examination of the entire series shows that there is a gradation from the common, through the indeterminate types to the uncommon.

The distribution of the records into these four categories is shown in the legend of Figure 1. It will be noted that there were 89 cases of the common type of intraventricular block. These included 10 cases of the concordant variety^{28b} where QRS was upright in all 3 limb leads, like the first line of Figure 1. The greater number had a contour like that seen in the second and third lines of Figure 1; however, 12 cases had QRS complexes directed up in the chest leads, as in the fourth line of Figure 1. Only 5 cases of the uncommon type were found, shown in the last line of Figure 1. There were 23 cases of the first indeterminate type of intraventricular block like the fifth line of Figure 1, and 59 cases were of the second indeterminate type of intraventricular block like the sixth and seventh lines of Figure 1.

(b) *By Etiology.* The cases were divided into four groups according to etiology as shown in Table 1. About one-fourth of the cases had evidence of recent or old myocardial infarction; about three-fifths fell into the arteriosclerotic group but without clear evidence of myocardial infarction. Many of the cases in these two groups also had hypertension. In our series there were relatively few cases with syphilitic and rheumatic heart disease. Other investigators have found a similar preponderance of arteriosclerotic heart disease.^{6 15 22 30 49 57 58}

TABLE 1.—DISTRIBUTION OF CASES OF INTRAVENTRICULAR BLOCK ACCORDING TO ETIOLOGY.

Clinical diagnosis	Average age, (yr)	% of total group	% of etiologic group in each electrocardiographic type			
			Common	Indeterminate Type 1	Indeterminate Type 2	Uncommon
Arteriosclerotic heart disease	61	62	49	13	35	3
Myocardial infarction (recent and old)	57	26	57	15	26	2
Syphilitic heart disease	51	6	40	20	10	0
Rheumatic heart disease	43	6	50	0	50	0
All types	58					

Of the 48 cases with myocardial infarction, 25 had electrocardiograms resembling the anterior wall type, 17 resembling the posterior wall type and 6 showed evidence of multiple infarctions (see Table 2). This table shows that there was no correlation between the type of block and the type of infarction shown in the electrocardiogram. This is in accord with previous observations.³⁹

TABLE 2.—INCIDENCE OF MYOCARDIAL INFARCTION (RECENT AND OLD) IN DIFFERENT TYPES OF INTRAVENTRICULAR BLOCK.

Type.	Total No. of cases.	No. of cases with each type of infarction.		
		Anterior.	Posterior.	Multiple.
Common	28	16	7	5 (ant. and post.)
Indeterminate Type 1	7	3	4	
Indeterminate Type 2	12	5	6	1 (mult. small)
Uncommon	1	1	0	
Totals	48	25	17	6

(c) *By Sex.* There were in our series 122 males and 54 females. This predominance of males is in accord with previous studies.^{1,7,15,—22,26,30,50,52,54,57,58}

(d) *By Age.* As expected, there was a definite age distribution according to the etiology of the intraventricular block (Table 1) but none according to the electrocardiographic pattern. The arteriosclerotic group had the oldest average age, 91% of this group being 50 years or over. Of the cases with myocardial infarction, 75% were 50 years or over. The syphilitic and rheumatic groups were much younger. This is in accord with previous findings from this department^{28a} and from other reports.^{4,7,13,15,19,20,22,23,25,26,30,34,45,50,52,—54,57,58,65}

In the entire series 64% of the cases were in the fifth and sixth decades (Table 3). The youngest case in this group was 25 years of age with rheumatic heart disease, the oldest 87 years with arteriosclerotic heart disease.

TABLE 3.—A COMPARISON OF AGE ACCORDING TO DECADES IN THE SERIES OF INTRAVENTRICULAR BLOCK.

Age (yrs.).	% of total group.	Age (yrs.).	% of total group.
Under 30	0.5	60 to 69	32.0
30 to 39	1.0	70 to 79	16.0
40 to 49	18.0	80 to 87	0.5
50 to 59	32.0	Average age, 58	

(e) *By Duration of QRS.* There was no definite relation between QRS duration and the type of electrocardiographic pattern, nor between QRS duration and the etiology of the block. The duration of QRS varied from 0.12 to 0.24 second and the average of the entire group was 0.135 second.

2. THE SIGNIFICANCE OF THE Q-E INTERVAL. In attempting to differentiate delay in the left ventricle from delay in the right, several investigators have employed optically recorded pulses taken simultaneously with Lead II. The rise in the pulse marks the onset of ejection of blood from the left ventricle plus the transmission time of the pulse to the spot recorded; the beginning of QRS indicates the onset of stimulation of the ventricles. Nichol⁴¹ designated the

difference between these two points, the $Q-E$ interval. He used the subclavian pulse for the former. He found that the $Q-E$ interval was prolonged in individuals with the common type of intraventricular block as compared with those with normal hearts. He interpreted this as indicative of delay in the left bundle. Wolferth

TABLE 4 — DURATION OF $Q-E$ INTERVAL IN 43 CASES OF VARIOUS TYPES OF INTRAVENTRICULAR BLOCK.

Type of intraventricular block	Illustrated in Fig 1.	Duration of QRS, sec	Duration of Q-E, sec	Average duration for group		Average duration for total group	
				QRS, sec	Q-E, sec	QRS, sec	Q-E, sec
Common	Line 1	0 16	0 18	0 160	0 180		
		0 12	0 20				
		0 12	0 16				
	Line 2	0 12	0 16	0 120	0 156		
		0 12	0 14				
		0 12	0 12			0 135	0 155
		0 16	0 18				
		0 22	0 24				
		0 16	0 17				
		0 12	0 16				
		0 12	0 16				
	Line 3	0 12	0 14	0 136	0 150		
		0 12	0 12				
		0 12	0 12				
		0 12	0 12				
		0 12	0 12				
		0 12	0 12				
	Line 4	0 16	0 19	0 145	0 170		
		0 13	0 15				
Indeterminate Type 1	Line 5	0 14	0 14	0 125	0 130	0 125	0 130
		0 12	0 14				
Indeterminate Type 2		0 12	0 12				
		0 12	0 09				
		0 12	0 11				
	Line 6	0 14	0 11	0 133	0 115		
		0 12	0 12				
		0 14	0 14				
		0 16	0 12				
		0 12	0 10				
		0 12	0 10			0 130	0 116
		0 12	0 10				
	Line 7	0 12	0 12	0 129	0 116		
		0 12	0 12				
Uncommon		0 14	0 12				
		0 14	0 12				
Uncommon	Line 8	0 14	0 14	0 153	0 120	0 153	0 120
		0 20	0 14				
		0 12	0 08				

et al.^{62,64} and others¹¹ arrived at much the same conclusion. We repeated this work some years ago²⁹ and concluded that "In intraventricular block: 1, a $Q-E$ of 0.18 second or longer suggests the presence of 'functional' left bundle branch block, but does not exclude the presence of 'functional' right bundle branch block; and that 2, a $Q-E$ interval of less than 0.14 second suggests the probable absence of 'functional' left bundle branch block and therefore suggests 'right bundle branch block'."

We pointed out further that due to various factors there is a considerable variation of the $Q-E$ interval in normal individuals.

Since our earlier report, we have carefully measured the $Q-E$ interval of 43 of our present series of 176 cases with intraventricular block. Each case was carefully checked and corrected for parallax when necessary. These measurements are shown in Table 4. The cases have been classed according to their resemblance to the records in Figure 1 and are summarized in Table 5. It is interesting to note in this table that 68% of the cases with the common type of intraventricular block had a $Q-E$ interval longer than the QRS , while 65% and 67% respectively of the cases of the second indeterminate and uncommon types of intraventricular block have a $Q-E$ interval shorter than QRS . It is also significant that 58% of the cases with the common type of block have a $Q-E$ longer than 0.14 second and 26% have one of 0.18 second or longer, while in none of the other three types is the $Q-E$ longer than 0.14 second and in about one-third of the second indeterminate and uncommon types, $Q-E$ is less than 0.12 second.

TABLE 5.—A COMPARISON OF QRS AND $Q-E$ INTERVALS IN DIFFERENT TYPES OF INTRAVENTRICULAR BLOCK.

Type.	Range of $Q-E$ interval duration in seconds.	Proportion of cases in each group with a $Q-E$ interval which is				
		Greater than QRS .	Less than QRS .	Less than average normal duration, 0.12 sec.	Greater than 0.14 sec.	0.18 sec. or longer.
Common	0.12 to 0.24	68%	0	0	58%	26%
Indeterminate Type 1	0.12 to 0.14	25%	0	0	0	0
Indeterminate Type 2	0.09 to 0.14	0	65%	35%	0	0
Uncommon	0.08 to 0.14	0	67%	33%	0	0

In order to get some idea of the trends, the $Q-E$ intervals of each of the four classes of intraventricular block were averaged and the results are presented in Table 6 listed under Series A. The cases previously published by us²⁹ were reclassified into these four classes and the averages in each are presented in Table 6 listed under Series B. The averages in each class in the two series compare closely. They show that only in the common type of intraventricular block is the $Q-E$ interval definitely beyond the average limits of the normal $Q-E$ interval. An interesting case in this connection was seen where a $Q-E$ interval was obtained before and after the development of intraventricular block. In this patient

when the *QRS* was normal in duration, 0.08 second, the *Q-E* interval was 0.14 second which is in the upper normal range. When intraventricular block of the common type developed with *QRS* 0.12 second in duration, the *Q-E* interval became 0.18 second.

TABLE 6.—VENTRICULAR DELAY IN THE DIFFERENT TYPES OF INTRAVENTRICULAR BLOCK AS DETERMINED FROM THE AVERAGES OF THE *Q-E* INTERVAL IN SEVENTY INDIVIDUALS.

Type of intraventricular block.	Series.	No. of cases.	Average duration of group in seconds.		Interpretation as to ventricular delay.
			<i>QRS</i> .	<i>Q-E</i> .	
Common	A	19	0 135	0 155	Left ventricle (Right ventricular delay is not excluded)
	B	16	0 143	0 164	
	Both	35	0 138	0 159	
Indeterminate Type 1	A	4	0 125	0 130	Undetermined
	B	2	0 120	0 130	
	Both	6	0 123	0 130	
Indeterminate Type 2	A	17	0 130	0 116	Right ventricle
	B	7	0 127	0 121	
	Both	24	0 129	0 118	
Uncommon	A	3	0 153	0 120	Right ventricle
	B	2	0 130	0 115	
	Both	5	0 144	0 118	
Normal adults	B	9	0 080	0 120	No delay

Series A = Present series (see Table 5).

Series B = Katz, Landt, and Bohning: *Am. Heart J.*, 10, 681, 1935.

All this evidence favors the idea that the common type of intraventricular block is most often associated with delay in the left ventricle and that the uncommon and the two indeterminate types are not associated with delay in the left ventricle, hence, presumably, with delay in the right ventricle. However, exceptions are found. Especially frequent is the lack of evidence of *Q-E* prolongation in the common type of intraventricular block. Our present deductions therefore in no way nullify our previous conclusions but are a further clarification of them.

THE AUTOPSIED MATERIAL. The data on the 25 cases coming to necropsy are summarized in Table 7. The autopsies were routine, and, while microscopic examinations of sections were made, no special studies of the relative involvement of the various parts of the conducting system were undertaken. Several of the complicating factors were revealed at necropsy, however, which may sometimes confuse the electrocardiographic picture. The actual curves of many of these have been published in earlier articles (see Table 7).

Of these cases, 19 had coronary sclerosis, 14 had myocardial infarction, 4 had syphilis and 1 of these latter had an anterior wall infarction. One, Case 22, had an active rheumatic infection and 3 showed evidence of old healed rheumatic lesions but associated with coronary sclerosis.

TABLE 7.—AUTOPSY FINDINGS IN 25 CASES WITH INTRAVENTRICULAR BLOCK.

Type of intra-ventricular block.	Figure illustrating type.	Case No.	Illustrated in figure.	Sex.	Age, yrs.	Duration of QRS, sec.	Etiologic factor.	Coronary artery involvement.		Valvular involvement.		Ventricles.		Septal involvement.		
								Right.	Left.	Mitral.	Aortic.	Tricuspid.	Hypertrophy.	Fibrosis.	Ocluded artery.	Common bundle
Common	Line 1	1	9 A of (1)	M	45	0.12	As	PL Thr	PL OPL	1	1		B			
		2	7 C of (1)	F	60	0.12	As						B	Apex		
	Line 2	3	7 B of (1)	M	43	0.12	As	OPL Thr	OPL S				L	Apex		
		4	6 B of (1)	M	65	0.12	As	OPL Thr	OPL S				L	Apex and base	1	
		5	6 A of (1)	M	63	0.12	As	OPL Thr	OPL S				L	Apex	1	
		6	Unpubl.	M	62	0.12	S	OPL Thr	OPL S				L	Apex		
		7	Unpubl.	M	64	0.12	S	OPL Thr	OPL S				L	Apex		
		8	Unpubl.	M	69	0.12	As	PL	PL	1			L			Necrosis
Indeterminate Type 1	Line 3	9	Unpubl.	M	48	0.16	As	PL	PL				B			
		10	9 E of (1)	M	79	0.16	As	PL	PL				L			
		11	3 A of (1)	M	45	0.12	As	N	OPL Thr	1			B	Apex	1	Fatty inflt.
		12	1 G of (1)	M	50	0.12	As	PL	PL				B	Apex	1	
Indeterminate Type 2	Line 4	13	2 D of (1)	F	58	0.12	As	OPL Thr	OPL S				L	Apex		
		14	4 C of (1)	M	50	0.12	As	OPL Thr	OPL S				B	Base		
		15	4 D of (1)	M	66	0.12	As	OPL Thr	OPL S				B	Base		
		16	Unpubl.	M	43	0.14	S	OPL Thr	OPL S				B	Base	1	Necrosis
Indeterminate Type 2	Line 5	17	1 F of (1)	M	58	0.12	As	N	Thr					Apex	1	
		18	Unpubl.	M	52	0.12	As	PL	PL				R		1	
		19	Unpubl.	M	81	0.12	As	PL	PL				B		1	
		20	Unpubl.	M	58	0.14	As	N	PL				B		1	
		21	Unpubl.	M	75	0.16	As	OPL	N				B		1	
		22	Unpubl.	F	40	0.14	RF	PL S.O.	PL S.N.	1			R	Base		
Indeterminate Type 2	Line 6	23	Unpubl.	M	70	0.12	As	PL S.O.	PL S.N.	1			R	Base	1	
		24	Unpubl.	M	44	0.16	S	PL S.O.	PL S.N.	1			R	Base		
		25	6 of (2)	M	57	0.12	As	PL S.O.	PL S.N.	1			L*	Base		
		25	6 of (2)	M	57	0.12	As	PL S.O.	PL S.N.	1			L*	Base		

(1) Arch. Int. Med., 61, 241, 1938.
 (2) Am. J. Med. Sci., 189, 233, 1935.
 R = Right ventricle.
 L = Left ventricle.
 B = Both ventricles.
 S = Syphilis (ostia of the coronary arteries).
 O = Occluded.
 As = Arteriosclerosis.
 RF = Rheumatic fever.
 * Fatty infiltration of right ventricle also present.
 PL = Plaque.
 OPL = Occluding plaque.
 S.O. = With.
 S.N. = Anterior.
 Thr. = Thrombosis.
 N = Narrowed.
 post. = Posterior.
 an'sm = Aneurysm.

There was no relation apparent between the location of the infarction and the type of intraventricular block. However, the infarct, old or new, leaves its impression on the record. This is discussed in another communication.⁹ Nor could any relationship be established in this series between the coronary artery involvement and the type of intraventricular block.

In 16 of these cases the septal involvement was visible grossly. In the cases of infarction this involved usually the left ventricular side of the septum adjacent to the infarct in the outer wall. In 1 (Case 17) there was an occlusion of the septal artery as well as that of the left anterior descending branch, and an anterior wall infarction. However, it must be recalled that in an earlier series of autopsied cases with myocardial infarction⁸ 6 cases with septal involvement were seen without electrocardiographic evidence of intraventricular block. Besides the cases with infarction, there were 4 with diffuse septal fibrosis and 4 had evidence of degeneration of the muscle fibers of the septum and 1 had "mummified" muscle fibers histologically in the septal area (Case 18). Two had necrosis involving the common bundle (Cases 7 and 13) and 1 had a fatty infiltration of the bundle fibers (Case 10).

Eleven cases had hypertrophy of both ventricles, 6 hypertrophy mainly of the left ventricle. In all but 2 of these last 6, the intraventricular block was of the common type. The exceptions had the first or second indeterminate types of intraventricular block; in the former, this was confined to his later records, the earlier ones being of the common type. There was another case besides this where a common type of block preceded the first indeterminate type. Nearly all cases showed myocardial fibrosis throughout both ventricles. There were 3 cases of hypertrophy confined to the right ventricle, all of the second indeterminate type.

This analysis of the 25 autopsied cases lead to the following main conclusion:

1. The chief causes for intraventricular block appear to be: (a) arteriosclerotic heart disease leading to degeneration of the fibers in the common bundle or a fibrosis of the ventricular muscle fibers in the septum and outer walls; (b) myocardial infarction involving the septal area, including old lesions and aneurysms; (c) occlusion of the septal artery or its branches; (d) syphilitic cardiovascular disease associated with narrowing of the coronary ostia, and with necrosis and fibrosis of the muscle fibers; (e) rheumatic heart disease associated with muscle fiber fibrosis.

2. There is no special electrocardiographic pattern associated with any particular etiologic factor, although left hypertrophy usually had the common, and right hypertrophy usually had the second indeterminate type.

3. Several etiologic factors are often present in the same case.

Our findings are in agreement with those of previous reports on necropsy material.^{3,21,30,36,38,39,51,56,66,67}

TABLE 8.—NUMBER OF INSTANCES OF EACH FORM OF DEFLECTION IN CF_2 AND CF_4 IN EACH TYPE OF INTRAVENTRICULAR BLOCK IN COMPLICATED CASES.*†

Type.	Total No. of cases.	CF_2 .										CF_4 .											
		QRS.										T.											
		V		A		V		A		V		A		V		A		V		A			
Common	$\begin{Bmatrix} 7 \\ 18 \\ 28 \\ 8 \end{Bmatrix}$	7	15	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Indeterminate Type 1	16	1	10	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Indeterminate Type 2	$\begin{Bmatrix} 10 \\ 37 \end{Bmatrix}$	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Uncommon	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Total number of cases with CF_2		128																					
		CF_4 .																					
Common	$\begin{Bmatrix} 3 \\ 11 \\ 14 \\ 2 \end{Bmatrix}$	3	7	3	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		
Indeterminate Type 1	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Indeterminate Type 2	$\begin{Bmatrix} 5 \\ 17 \end{Bmatrix}$	1	4	11	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2		
Uncommon	4	1	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		

* The 48 cases of definite myocardial infarction are excluded from this table.
 † Taken in accordance with modern method for chest leads (upward deflection represents relative positivity).
 iso = iso-electric.

CHEST LEAD VARIATIONS IN THE DIFFERENT TYPES OF INTRA-VENTRICULAR BLOCK. The data as to the configuration of the two chest leads, CF_2 and CF_4 , used by us routinely, in the various types of intraventricular block uncomplicated by myocardial infarction, are shown in Table 8. In Figure 1 is summarized the prevalent appearance of these 2 chest leads together with the limb leads in the different types of intraventricular block. Examination of this table and this figure will show that a definite pattern is found in the chest leads and that the chest leads can help to substantiate the type of intraventricular block identified in the limb leads. That exceptions and intermediate forms occur is not surprising since associated conditions can alter the electrocardiographic pattern. Among the most important is myocardial infarction.⁹

In the common type of intraventricular block, QRS may be entirely down in both of these chest leads, often with a preliminary small upright phase. Less commonly, QRS is entirely up in both chest leads, sometimes with a tiny inverted preliminary phase in CF_4 . It is unusual to find QRS down in CF_2 and upright in CF_4 , or to find an equiphasic QRS in CF_4 with the first phase up. The $S-T-T$ in these chest leads almost without exception is opposite to the major phase of QRS .

In the first indeterminate type, QRS is upright in both CF_2 and CF_4 and usually there is both a preliminary and final inverted phase of some magnitude. Sometimes the preliminary phase is absent, sometimes the inverted phases are so large as to give a W appearance to the QRS . Rarely an M type of curve may be seen in CF_2 . $S-T-T$ is practically always directed downward.

In the second indeterminate type, QRS in CF_2 is of the M type with the deflection almost entirely up, although occasionally the middle phase may go below the isoelectric level. Sometimes the first phase of the M is so large and the third so small that it takes on the appearance of notching on the downstroke. On rare occasions QRS may be polyphasic. $S-T-T$ in this lead with these configurations is practically always downwardly directed. Some cases of this type show QRS diphasic with the second phase inverted and prolonged; here $S-T-T$ is directed upward. This last is the usual appearance of the $QRST$ in CF_4 . Occasionally an M type may be seen in both CF_2 and CF_4 .

In the uncommon type, the forms are similar to those seen in the second indeterminate type except that the M type is not seen in CF_4 and the diphasic type is more common than the M type in CF_2 .

Summary. An analysis was made of the electrocardiograms of 176 individuals with intraventricular block. They were classified according to the differences in pattern found in the limb and chest leads. The types were related to the probable delay in stimulation

of the right and left ventricle, as suggested by the averages of the *Q-E* intervals (the time from the onset of *QRS* to the rise of the subclavian arterial pulse) in each group. Further, an analysis of some detail was made of the findings in 25 autopsied cases.

Conclusions. 1. Intraventricular block occurs more frequently in males and most often in the fifth and sixth decades of life.

2. Arteriosclerotic heart disease was the most frequent etiologic factor in intraventricular block in our series; syphilitic and rheumatic heart disease were responsible for the smaller number of cases.

3. Intraventricular block in the autopsied group of cases was associated with:

(a) Involvement of the common bundle or some of its major branches as a result of arteriosclerotic or syphilitic disease.

(b) Involvement of the septal muscle fibers by infarction, fibrosis or degenerative processes.

(c) Involvement of massive character of the myocardium of the ventricles by degenerative processes accompanying arteriosclerotic, syphilitic or rheumatic heart disease.

(d) Involvement of several areas by the above etiologic processes.

4. Intraventricular block is diagnosed in the electrocardiogram by finding a *QRS* duration of 0.12 second or longer in the limb leads. Examination of the records shows that they can be grouped into four types, the common, the uncommon, and the first and second indeterminate types.

5. While other influences such as hypertrophy and displacement of the heart, as well as the causes which lead to low voltage, affect the appearance of the electrocardiograms in intraventricular block, the various types, by and large, appear to represent definite types of delay in the spread of the impulse, viz:

(a) The common type of intraventricular block appears to represent chiefly delay in the left ventricle.

(b) The uncommon and second indeterminate types of intraventricular block appear to represent chiefly delay in the right ventricle.

(c) The first indeterminate type of intraventricular block appears to represent a mixture of delay in the right and left ventricles.

6. These studies confirm and expand the views developed by us previously regarding intraventricular block.

7. The characteristic appearance of the electrocardiogram in *CF*₂ and *CF*₄ is described (and the typical contour is shown in Fig. 1) for each of the four types of intraventricular block into which all cases appear to fall.

We are indebted to several interns of the department for their assistance in obtaining the electrocardiograms and to Dr. O. Saphir of the Department of Pathology whose postmortem interpretations were used in our analysis of the 25 autopsied cases. We are indebted to the various physicians for their kind permission to use the records of their patients.

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PHONOGRAPH RECORDS OF HEART SOUNDS, MURMURS AND ARRYTHMIAS.

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SOME 15 or 16 years ago, Gamble and Cabot¹ made a series of heart records somewhat in the nature of case reports. There was recited a short history, a résumé of physical findings and diagnosis of the case and then followed the specific heart sounds and murmurs of that case. Unfortunately, due to the stage of development of recording and of reproducing in those days, it was very difficult to play these back with the home phonograph then in use and they were not satisfactory.

The value of physical findings in cardiac diagnosis has been overshadowed in the past few years by the development of graphic methods. While we all are grateful for the contribution that electrocardiographic and radiologic diagnosis has made in our present-day advance, it seems that this very advance has tended to lessen interest in auscultatory findings. Furthermore, no one will deny that stethocardiograms, vital capacity studies and various laboratory procedures are valuable particularly from an investigative standpoint; but all such studies are of little help in the run-of-the-mine clinical case. This is particularly true in the younger age groups with which the family physician has to deal. As Wolferth and Margolies² aptly stated: "There seems to have been a tendency in recent years to minimize the value of auscultation; one frequently observes it done in a perfunctory manner. Nevertheless, in spite of all the advances that have been made in other directions, there is just as great need today as there was in Potain's time for physicians to train themselves rigorously in auscultation. As knowledge regarding heart sounds has increased, the information that may be derived from auscultation has also increased" and "it is safe to say that at this time sounds which cannot be detected by the examiner with ordinary hearing ability and good training are of no great clinical significance. It is much more important to be able to tell which of the audible sounds are significant and which are not."

With present-day methods of recording and the perfection of reproduction (the cheapest radio-phonograph will give satisfactory results), it is somewhat strange that more attempts have not been made to utilize this method in teaching. Phonograph records are particularly adapted for teaching in that the same illustration may be reproduced as often as desired and repetition is the secret of any good teaching. Furthermore, the record can be well heard by a class of any size. It has already been satisfactorily demonstrated in an auditorium with good acoustics to over 300 people.

In collaboration with the Columbia Recording Corporation, a series of records of all types of auscultatory signs was developed. The following have been selected, 6 or 7 to a record, with frequent interpolation of normal heart sounds for easy comparison.

<i>Sounds</i>	<i>Murmurs</i>	<i>Arrhythmias</i>
Normal first and second sounds at the apex	Blowing systolic murmur of moderate pitch; normal sinus rhythm	Premature systoles
Reduplicated first sound	Blowing systolic murmur with auricular fibrillation	Coupling
Reduplicated apical second sound	Harsh systolic murmur with loud second sound	Auricular fibrillation
Apical first sound louder than the second sound	Harsh systolic murmur with doubled second sound	Auricular fibrillation with exercise
Tic-tac sounds	Harsh systolic murmur replacing first sound	Auricular fibrillation with premature systoles
Normal first and second sounds at the apex	Harsh systolic murmur with auricular fibrillation	Sinus arrhythmia
Accentuated aortic second sound	Loud harsh musical systolic murmur	Typical gallop rhythm
Ringing aortic second sound	Squeaky systolic murmur	Atypical gallop rhythm
Accentuated pulmonic second sound	Harsh aortic systolic with a diastolic murmur	
	Faint mid-diastolic murmur	
	Very faint apical diastolic murmur	
	Long low-pitched diastolic murmur	
	Mitral diastolic murmur with presystolic accentuation	
	Diastolic murmur with presystolic accentuation and a sharp first sound	
	Diastolic decrescendo murmur	
	Both sounds replaced by murmurs	
	Comparison of syphilitic and rheumatic aortic murmurs	
	"Machinery-like" murmur of a patent ductus arteriosus	

An appropriate explanation introduces each illustration, to point out its significant features and to suggest what to listen for. Only one feature of an illustration is emphasized; any other abnormality is mentioned but not stressed. Considerable thought was given to the length of the illustration; if too long, it becomes tiresome; if too short, it does not sufficiently drive home the feature one hopes to demonstrate. The nomenclature suggested by the American Heart Association is used. A unique feature of these records is that the level of the spoken voice and the loudness of the illustration was

so adjusted that if instructions are followed the illustrations are heard with the same intensity and quality of sound as was heard with the stethoscope on the patient's chest when the recording was made. Extraneous noises which interfere with the illustration were for the most part eliminated, but it was thought inadvisable to remove all breath sounds, and so on because actually when one listens to a patient these are heard with heart sounds and the reproduction seems more real. Records of rare and obscure abnormalities were included as well as those which could be easily heard and distinguished. Several, such as the mid-diastolic murmur heard in a case with beginning mitral stenosis, are difficult to hear but for that reason are probably most valuable from a teaching standpoint. In a given case under examination they represent that type of finding which must be sought after and which does not present itself readily. The records also have value in their veracity and because they train one to listen more intently.

These records do well for self-teaching as well as for class work. One listens with his stethoscope as the record is being played, simply holding the chest piece in his hand with the bell or diaphragm exposed to the air. It is suggested that one sit comfortably in a quiet room and close one's eyes (it always helps to blot out as many sensory stimuli as possible).

It is hoped that these records will fill the need of the family physician who has been away from a center for a number of years and who needs a "refresher." They are of value in Undergraduate and Post-Graduate teaching; and they may have value to Draft Board examiners. Because of their inclusion of even rare auscultatory abnormalities, they are of use for reference.

Much credit must go to the officials and sound engineers of the Columbia Recording Corporation without whose efforts and interest this work would have been impossible. Their assistance was largely responsible for the "high fidelity" of the records.

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A SIMPLE MICRO-TEST FOR SULFANILAMIDE AND ITS DERIVATIVES IN BLOOD.*

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SAFE and efficient therapy with sulfanilamide or any of its derivatives is greatly facilitated by frequent determinations of the

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drug level in the blood. Such determinations, however, are not performed as widely and as often as indicated, being limited mainly to those who have the services of a hospital or a private laboratory at their disposal. The methods used at present for determination of sulfanilamide compounds are still too complicated to be applied routinely outside of the laboratory. In addition, most of these methods require from 0.5 to 2 cc. of blood for a single analysis, an amount which necessitates a venipuncture. This constitutes a further deterrent when frequent analyses are performed. Micro-methods which utilize 0.1 cc. of blood, for one determination, and thus can be performed on finger blood, have been devised. However, almost all of them employ a photoelectric colorimeter. The bedside micro test proposed by Schoeffel⁹ substitutes direct comparison of color on absorption paper for colorimetric measurements, but otherwise does not materially simplify the technique.

Method. The method presented below requires 0.1 cc. (approximately 2 to 3 drops) of blood for a single analysis. It is the micro-modification of a test¹ based upon the methods of Kühnau⁷ and of Werner¹¹ which employ the yellow color formed by reaction of sulfanilamide (and its derivatives) with para-Dimethylaminobenzaldehyde in acid medium. We have found that by the addition of alcohol the intensity of color is considerably increased and, to a great extent, made independent of changes in acidity of the medium.⁴ A further improvement was achieved by the use of a blue glass filter⁸ which eliminates the difficulty of comparing yellow colors by turning them into various shades of blue-green. The test can be performed in 6 to 8 minutes and is extremely simple. It can be applied equally well by the technician in the laboratory and by the physician at the patient's bedside. Parallel determinations of drug level by the present micro-method and the standard method of Bratton and Marshall² on 93 blood specimens obtained from patients receiving one of the sulfanilamide compounds (sulfanilamide, sulfapyridine or sulfathiazole) showed very close agreement, the average difference being 0.5 mg. per 100 cc., the maximum difference being 1 mg. per 100 cc. Because of its time and labor saving qualities without loss in accuracy, as compared to diazotization procedures commonly applied, the method is now being used routinely in the laboratory of this hospital. The results are very satisfactory.

Reagents.* A. 15% aqueous solution of trichloroacetic acid.

B. 2% para-Dimethylaminobenzaldehyde† (p-BA) in 95% ethyl alcohol. (If stored in a glass-stoppered brown bottle the reagent keeps for at least a month. It is almost colorless, if prepared from fresh p-BA. Crystalline substance which has turned strongly yellow due to prolonged standing is unsuitable for use.)

C. N/6 HCl (for determination of total sulfanilamide concentration).

Equipment.‡ A. Test tubes, 10 mm. in diameter, calibrated at 1.5 cc., 2 cc., 3 cc. and 4 cc., with rubber stoppers.

B. Blood pipette, 0.1 cc.

C. Small (1 inch) funnel and filter paper (Whatman No. 2, 4.25 cm.).

* The reagents are conveniently kept in dropper bottles.

† para-Dimethylaminobenzaldehyde may be obtained from Eastman Kodak Company, Rochester, N. Y.

‡ All equipment, including slide comparator with permanent sulfanilamide standards, is manufactured by W. A. Taylor & Co., Baltimore, Md.

D. Graduated centrifuge tubes (for determination of total sulfanilamide concentration).

E. Comparator (block or slide) with blue glass filter, a set of permanent standards (Table 1) and comparison tubes (10 mm. inside diameter) calibrated at 1 and 1.5 cc.

TABLE 1.—COMPOSITION OF PERMANENT NON-FADING STANDARDS.

$K_2Cr_2O_7$, 0.1% (Cc.)	K_2CrO_4 , 0.25% (Cc.)	H_2O , (Cc.)	Corresponding concentrations of sulfanilamide in blood. (Mg. per 100 cc.)
0.5	0.1	9.4	0
1.0	0.25	8.75	1
1.5	0.4	8.1	2
1.9	0.5	7.6	3
2.2	0.7	7.1	4
2.5	0.9	6.6	5
2.7	1.3	6.0	6
3.0	2.1	4.9	8
3.0	3.7	3.3	10
	0.5%		
3.0	5.0	2.0	15

Procedure. A. *Determination of Free Sulfanilamide.* 1. Place 1.5 cc. of water in the calibrated test tube.

2. Add 0.1 cc. of blood (drawn from finger or ear lobe) and rinse the blood pipette several times with the water in the tube. Shake the tube gently for a minute or two until the blood is completely hemolyzed.

3. To precipitate the proteins, add 15% trichloroacetic acid up to the 2 cc. mark (approximately 8 drops). Close the tube with a rubber stopper and invert several times. This step may be performed immediately following 2, or within several hours.

4. After 2 minutes filter the mixture directly into the comparison tube up to the 1 cc. mark. Instead of filtering, the mixture in the precipitation tube may be centrifuged for 5 minutes at high speed, and 1 cc. of clear supernatant fluid transferred to the comparison tube by means of a capillary pipette. This is especially convenient if several tests are run simultaneously.

5. Add the p-BA reagent up to the 1.5 cc. mark, mix by inversion, and compare with the standards in the comparator, either immediately or within 2 hours. In the latter case the comparison tube must be tightly stoppered.

The p-BA reagent should be shaken before use.

If the drug level in the blood is found to exceed 10 mg. per 100 cc., accurate determinations are obtained by repeating the test with double dilution of the blood. For that purpose 0.1 cc. of blood is hemolyzed in 3 cc. of water and trichloroacetic acid added up to the 4 cc. mark (about 18 drops). Otherwise the procedure remains unchanged. The readings are multiplied by 2.

B. *Determination of Total Sulfanilamide.* The procedure as described above remains unchanged up to Step 4. Steps 4 and 5 are modified as follows:

4. Place 1 cc. of the filtrate or centrifugate in a graduated centrifuge tube, add 1 cc. of N/6 HCl, mix, and heat in a boiling water bath for 1 hour in order to hydrolyze the acetylated sulfanilamide. The mixture evaporates almost completely. Cool to room temperature and bring the volume up to 1 cc. with water.

5. Add the p-BA reagent up to the 1.5 cc. mark, mix by inversion, transfer into a comparison tube and compare with the standards. The readings are then multiplied by 1.15 to compensate for the decrease in color intensity due to the addition of hydrochloric acid.

C. Determination of Sulfanilamide Derivatives. With appropriate standards the test can be applied equally well to the determination of sulfapyridine, sulfathiazole, and other sulfanilamide derivatives. For clinical purposes, sufficiently accurate results can be obtained with these compounds by using the sulfanilamide standards for comparison, provided the readings are multiplied by the following factors:

	Free.	Total.
Sulfapyridine	1.5	1.7
Sulfathiazole	1.7	2.0

These factors take into account the higher molecular weight of sulfapyridine and sulfathiazole, the loss in precipitation due to the poor solubility of these compounds, and, in determination of total drug concentration, also the decrease in color intensity caused by the addition of hydrochloric acid.

Sources of Error. Similar to the diazo-reaction, the color developing with p-BA is not specific for the compounds of the sulfanilamide series but is also given by many aromatic amines, *e. g.*, novocaine.^{3,10} In addition, p-BA forms a yellow color also with urea⁶ and with aliphatic amines except for α -amino-acids.¹⁰ Significant interference can only be expected from the presence of novocaine and other therapeutic agents of similar structure; whereas, in the case of urea, the color is about 300 times weaker than that of sulfanilamide and will, therefore, even in the presence of severe azotemia, cause errors no greater than 0.5 to 1 mg. per 100 cc. of sulfanilamide. No interference can be expected from aliphatic amines in body fluids. Likewise, the presence of bile pigments in the blood has no influence upon the readings, as these pigments are removed with the proteins.

Summary and Conclusions. A micro test for the determination of sulfanilamide and its derivatives in blood is presented. It is based upon the yellow color resulting from the reaction between sulfanilamide and p-Dimethylaminobenzaldehyde, which has been stabilized and intensified by the addition of alcohol. Readings are facilitated by the use of a blue filter.

The rapidity and simplicity of the procedure make the test especially applicable to determinations at the patient's bedside. Because of the small amount of blood (0.1 cc.) required for a single analysis, the test is particularly convenient for frequent determinations in the clinical laboratory as well as in experiments with small laboratory animals.

In 93 parallel determinations on human blood specimens, the average difference of values obtained with the method of Bratton and Marshall and the present micro-method was 0.5 mg. per 100 cc. and the maximum difference 1 mg. per 100 cc.

The standards are prepared by mixing aqueous solutions of potassium dichromate ($K_2Cr_2O_7$) and potassium chromate (K_2CrO_4) with water, as given in Table 1. The final mixtures are transferred into comparison tubes (ampoule form, 10 mm. inside diameter) and sealed.

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THE EFFECT OF LOW CALCIUM DIET AND CALCIFEROL (VITAMIN D₂) ON CALCIUM AND PHOSPHORUS METABOLISM.

STUDIES ON TWO PARATHYREOPRIVIC PATIENTS AND ONE "NORMAL" SUBJECT.

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THE irradiation of ergosterol with ultra-violet light produces a series of secondary sterols, at least two of which, calciferol (vitamin D₂) and tachysterol, exert a marked effect upon the metabolism of calcium and phosphorus. The action of these two substances has been studied in detail by a number of observers during recent years.^{2,7,9,12} Thus in a comparative study Albright and his co-workers² concluded that both calciferol and dihydrotachysterol (a derivative of tachysterol) increase the urinary excretion of phosphorus and the intestinal absorption of calcium with the ultimate result that the concentration of calcium in the serum is increased and that of inorganic phosphorus in the serum is decreased. They state that "the ratio of the effect on phosphorus excretion to that on calcium absorption is greater with AT10 (*dihydrotachysterol*) than with Vitamin D;" they offer this fact as the possible explanation of the lack of antirachitic effect of dihydrotachysterol. Both these substances have proven highly effective when administered orally in the treatment of parathyroid insufficiency, particularly in the chronic forms in which the patient frequently becomes refractory to parathyroid extract. The addition of extra calcium to the diet

is usually unnecessary. The effective dose of calciferol generally varies from 6 to 12 mg. (200,000–400,000 vitamin D units) per day.

The effects of large doses of irradiated ergosterol upon calcium and phosphorus metabolism in the normal adult have been studied by Bauer, Claffin and Marble.⁵ They observed an initial temporary increase in the fecal excretion of calcium and phosphorus at the expense of the urinary excretion; this was immediately followed by a marked reduction in fecal excretion of these elements and a marked rise in their urinary excretion, without significant change in the total balance of either calcium or phosphorus. These changes did not depend upon the amount of calcium ingested or upon the calcium: phosphorus ratio of the diet. Only slight changes occurred in the concentration of calcium and inorganic phosphorus in the serum.

We wish to report observations upon 2 patients suffering from chronic parathyroid insufficiency and upon one subject presenting no evidence of abnormal calcium or phosphorus metabolism.

All of these patients received large doses of calciferol* while on a diet low in calcium. The patients were maintained throughout the period of study upon diets based upon the recommendation of Bauer and Aub.⁴ The diet as offered to the patients consisted of the following:

Morning: 40 gm. bread
100 gm. orange juice
30 gm. bacon
20 gm. jelly or honey
5 gm. sugar
100 gm. farina
Coffee
Noon: 100 gm. steak or lean meat
100 gm. potato
100 gm. corn
40 gm. bread
200 gm. apple
10 gm. jelly or honey
5 gm. sugar
Tea
Evening: 30 gm. chicken
100 gm. corn
100 gm. tomatoes
100 gm. peaches
40 gm. bread
10 gm. jelly or honey
5 gm. sugar
Tea

This diet contains approximately 58 gm. protein, 32 gm. fat and 230 gm. carbohydrate, representing 1440 calories per day.

The calcium and phosphorus content of all rejected food was calculated¹⁴ and the total daily intake of calcium and phosphorus was determined by subtracting these figures from the calculated total content of the daily

* The calciferol used in this study was donated by the Department of Medical Research of the Winthrop Chemical Company, Inc., in the form of capsules of Drisdol Concentrated Solution in oil. Each capsule contained 50,000 units of vitamin D.

8.3 to 5.5 mg. per 100 ml. in 6 days after the withdrawal of the daily dose of 16 teaspoonsful of calcium lactate and 10 minims of viosterol. Roentgen rays taken October 17, 1939, 29 days after the institution of the calcium-poor diet, showed no evidence of decalcification in the skull, spine, pelvis, upper extremities and femora.

The significant changes observed in this patient may be summarized as follows:

1. Delay in the appearance of marked parathyreoprival symptoms together with failure of the concentration of serum calcium to decrease significantly for 33 days, except for the initial fall which immediately followed the institution of the low calcium diet. It should be noted that the concentration of inorganic serum phosphorus likewise failed to increase significantly during the same 33-day period.

2. The maintenance of a negative calcium balance and a slightly positive phosphorus balance prior to the administration of calciferol. During this period the urinary excretion of calcium was about half that of the fecal content.

3. A rise in concentration of serum calcium beginning by the 6th day after the institution of calciferol therapy and continuing to the 20th day of treatment.

4. A gradual fall in the concentration of inorganic serum phosphorus beginning by the 6th day and reaching a minimal level by the 17th day of calciferol therapy.

5. A gradual, progressive increase in urinary calcium excretion following calciferol therapy with a corresponding decrease in fecal calcium so that the negative calcium balance persisted.

6. A shift of generally similar character in phosphorus excretion following calciferol therapy, with persistence of the positive phosphorus balance.

7. The gradual development of parathyreoprival symptoms on the low calcium regimen without medication with relief beginning within 4 days after the institution of calciferol therapy and progressing thereafter as the concentration of serum calcium increased.

Since discharge from the hospital the patient has remained on an unrestricted diet. She received 300,000 units of vitamin D₂ daily until August 16, 1940, and during this period she remained well and the serum calcium and inorganic phosphorus remained within normal limits. On August 16, 1940, she reported to the Outpatient Clinic complaining of anorexia, weakness, loss of weight and tachycardia. On this date, the serum [calcium] was 16 mg. per 100 ml. and the inorganic [phosphorus] was 3.2 mg. per 100 ml. The administration of calciferol was immediately stopped and the patient received no medication until October 8, 1940, at which time the serum [calcium] was 10.3 and inorganic [phosphorus] 3.1 mg. per 100 ml. From that date until the time of writing (May 28, 1941) the daily dose of calciferol has been 200,000 units

diet. It should be noted that this diet lacks vitamin D. No medication except calciferol was given to any of the subjects. Analyses of samples of a hashed daily diet yielded 160 mg. of calcium and 768 mg. of phosphorus. The patient's hospital stay was divided into 3-day periods during which all urine and feces were collected and separately pooled. The limit of each 3-day period for the collection of feces was determined by the appearance of carmine in the stool. Samples of serum from venous blood were collected at the beginning of each 3-day period and at the end of the study except in the control subject (see below). The concentrations of calcium and inorganic phosphorus were determined by the method of Clark and Collip⁶ and Tisdall,¹⁷ respectively. The protein values were calculated from specific gravity measurements according to the method of Moore and Van Slyke.¹⁰ The calcium content of each pooled specimen of urine and feces was determined by the method of Shohl and Pedley¹⁶ and the inorganic phosphorus content of these specimens by the method of Tisdall.¹⁷ In Subject J. P., the concentration of organic phosphorus in the urine was likewise determined.

The 2 patients with parathyroid insufficiency had been under treatment prior to the beginning of our study. Patient L. H. had been taking from 8 to 12 teaspoonsful of calcium lactate and 10 minims of irradiated ergosterol daily. Patient J. J. had been taking 2 ml. of dihydrotachysterol 3 times weekly. All medication was withdrawn from both these patients before the beginning of this study. When the concentration of calcium in the serum had reached a level at which symptoms of tetany became prominent, the daily administration of 400,000 units of vitamin D₂ (10 mg. calciferol) was begun and continued thereafter throughout the period of study. Subject J. P., who presented no evidence of abnormal calcium or phosphorus metabolism, received the same daily dose of calciferol after four periods of observation without medication.

Case Reports. CASE 1.—J. J., a married mulatto woman, aged 40, had suffered from chronic parathyroid insufficiency since a subtotal thyroidectomy performed elsewhere for hyperthyroidism in 1927. Her treatment since that time had included large doses of calcium by mouth, low phosphorus diet, viosterol, parathyroid extract and, more recently, dihydrotachysterol. The effect of dihydrotachysterol in this patient has been reported by two of us in a previous communication.¹² For 24 months prior to the beginning of the present study the [calcium]* and inorganic [phosphorus] in the serum had been maintained at normal levels and her symptoms had been satisfactorily controlled by the administration of 2 ml. of dihydrotachysterol (10 mg.) 3 times a week; her diet had been unrestricted. Bilateral lenticular opacities were present. There was a small firm mass of recurrent thyroid tissue. Tachycardia was occasionally present, but the basal metabolic rate remained consistently within normal limits. Dihydrotachysterol was withdrawn on October 10, 1939, and the patient was admitted to the medical division of the Hospital on October 17, 1939, where she remained until December 16, 1939. Her hospital stay comprised nineteen 3-day periods. The results of our observations are shown graphically in Figure 1. It is of interest that while the calcium in the serum fell from 9.1 to 7.6 mg. per 100 ml. within 3 days after the institution of the low calcium diet, it did not change significantly thereafter for 33 days, at which time it reached a low point of 7.2 mg. per 100 ml. coincidentally with severe parathyreoprival symptoms. This was 43 days after the withdrawal of dihydrotachysterol and 36 days after the beginning of the low calcium diet. This slow decline is in sharp contrast to the rapid fall in serum calcium observed when this same patient was studied after the withdrawal of oral calcium therapy in 1937. At that time the serum [calcium] fell from

* [] denote concentration.

other day was stopped on February 14, at which time the concentration of calcium in the serum was 10.3 mg. per 100 ml. and that of inorganic phosphorus in the serum was 3.2 mg. per 100 ml. The subsequent decline in serum [calcium] and the rise in inorganic serum [phosphorus] were slow. The concentration of calcium in the serum did not fall below 8.5 mg. per 100 ml. until March 27 (41 days after the withdrawal of dihydrotachysterol) at which time it reached 6.9 mg. per 100 ml. and symptoms of tetany for the first time became severe. The concentration of inorganic phosphorus

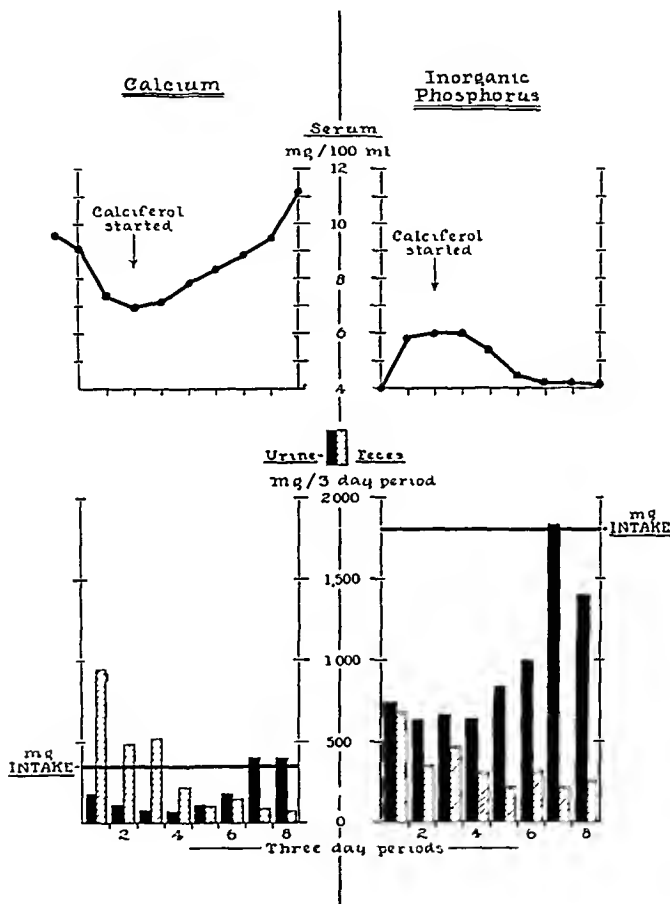


FIG. 2.—Patient L. H. (chronic hypoparathyroidism).

in the serum was 5.5 mg. per 100 ml. on this date. From March 28, 1939, until December 29, 1939, the medication consisted of large doses of vitamin D₂ (200,000 to 300,000 units daily) with occasional, irregular, self-administered doses of calcium. In July, 1940, an artificial menopause was induced by irradiation because of menorrhagia associated with multiple uterine fibroids. Because the patient believed that she felt better when taking calcium, the large doses of vitamin D₂ were stopped on December 29, 1939, and from this date until the beginning of the present study her medication consisted of from 8 to 12 teaspoonfuls of calcium lactate with 10 min-

of vitamin D. It may be noted that her present maintenance dose of calciferol is 35 mg. weekly as compared with a previous satisfactory maintenance dose of dihydrotachysterol which was 30 mg. weekly.

CASE 2.—L. H., an unmarried white woman, aged 47, underwent a subtotal thyroidectomy for hyperthyroidism elsewhere in 1923. This was followed by bilateral paralysis of the recurrent laryngeal nerves, necessitating a tracheotomy, and by severe symptoms of parathyroid deficiency. The patient was first seen by us in 1927, at which time bilateral lenticular opacities were found. There has been little change in these to date. The

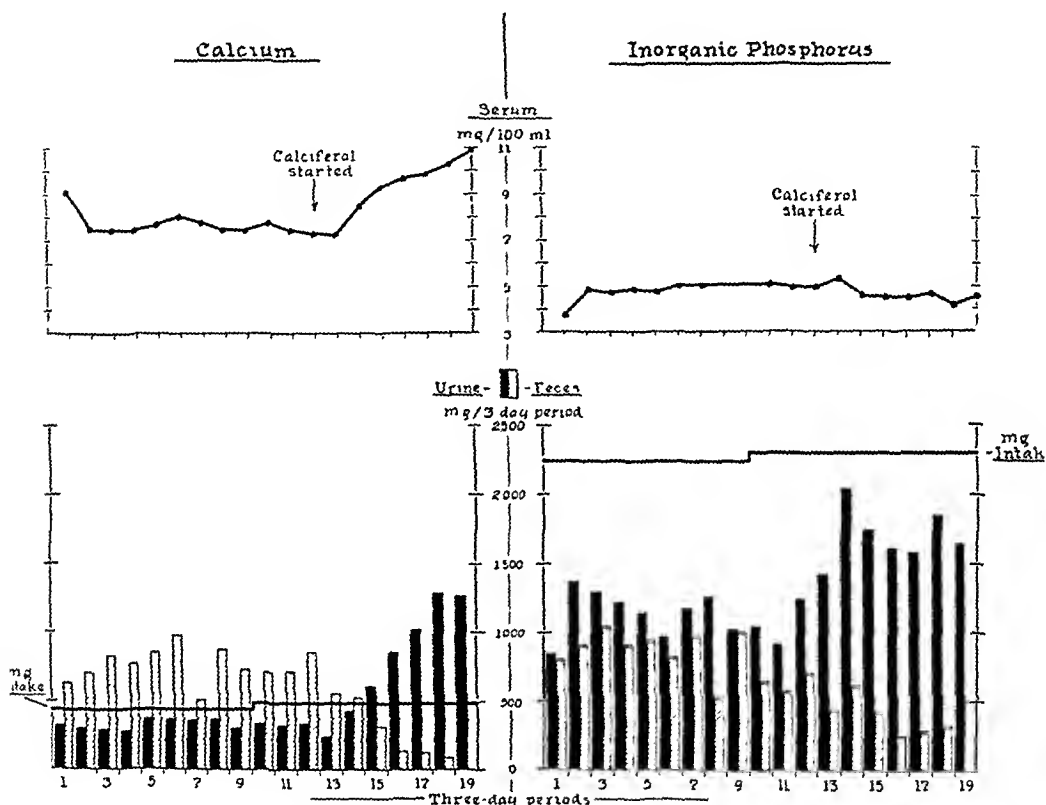


FIG. 1.—Patient J. J. (chronic hypoparathyroidism).

In Figures 1, 2 and 3 are shown the amounts of calcium and phosphorus ingested per 3-day period; the urinary and fecal excretion of calcium and inorganic phosphorus per 3-day period; and the concentrations of calcium and inorganic phosphorus in the serum before and during the daily administration of 400,000 vitamin D units of calciferol.

patient has been under continuous observation since 1927. Two parathyroid transplants were made in 1928, with little, if any, benefit. Therapy had included large doses of calcium, vitamin D, parathyroid extract, desiccated thyroid, a diet low in phosphorus and the administration of dihydrotachysterol. The effect of dihydrotachysterol in this case has been described by two of us in a previous communication.¹² The patient's symptoms were fairly well controlled by a combination of large doses of calcium and small doses of dihydrotachysterol from December 20, 1937, to February 14, 1939. She was unable to afford an adequate dose of dihydrotachysterol. From February 14 to March 29, 1939, she received no therapy. The daily dose of 10 teaspoonfuls of calcium lactate and 1 ml. of dihydrotachysterol every

at intervals of 7 days thereafter. On the 13th day of study the daily administration of 400,000 vitamin D units of calciferol was begun and continued until the end of the period of observation. Our findings are shown in Figure 3.

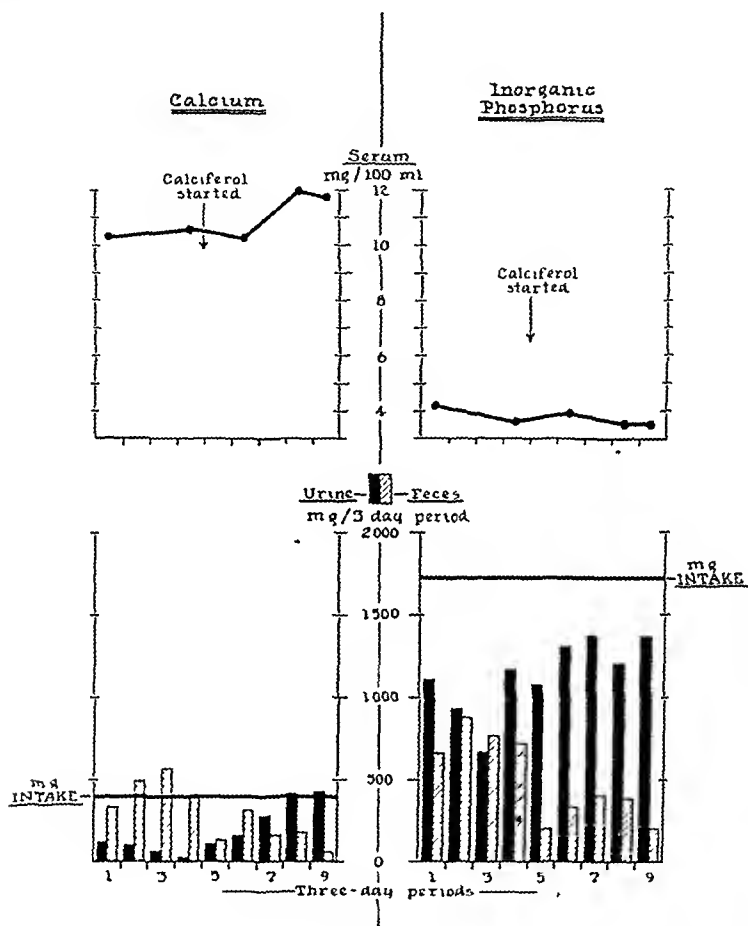


FIG. 3.—Patient R. P. (myotonia atrophica; no evidence of parathyroid disease)

The significant changes observed may be summarized as follows:

1. An increase in the concentration of serum calcium which followed the administration of calciferol and reached a maximum by the 15th day of therapy.

2. A slight, gradual, irregular decline in the concentration of serum inorganic phosphorus, beginning after the administration of calciferol and reaching a minimum by the 15th day of therapy.

3. The maintenance of a negative calcium balance throughout the period of observation.

4. The maintenance of approximate phosphorus equilibrium throughout the period of observation.

ins of viosterol daily; the diet was unrestricted. On this regimen her symptoms were fairly well controlled and the serum [calcium] varied from 8.6 to 10.7 mg. per 100 ml. and the serum inorganic [phosphorus] from 3.4 to 4.2 mg. per 100 ml. All medication was stopped on September 17, 1940, and on this date the patient was readmitted to the hospital where she remained under observation until October 15, 1940. She was kept on a low calcium diet as previously indicated. By September 26 the serum [calcium] had fallen to 7 mg. per 100 ml., and symptoms of parathyroid insufficiency had risen to 6 mg. per 100 ml., and symptoms of parathyroid insufficiency were prominent. On September 27, the daily administration of 400,000 vitamin D units of calciferol was begun and continued regularly until the end of the period of study October 15, 1940. The results of our observations are shown in Figure 2.

The significant changes observed may be summarized as follows:

1. A fall in the concentration of serum calcium and coincidental appearance of symptoms of tetany following the withdrawal of calcium therapy in a much shorter time than the similar changes observed after the withdrawal of dihydrotachysterol.
2. A generally negative calcium balance except during the second, third and fourth periods following the institution of calciferol therapy.
3. The maintenance of a generally positive phosphorus balance throughout the period of study.
4. A rise in the concentration of the serum calcium beginning by the 3d day after the institution of calciferol therapy and reaching a maximum by the 18th day of treatment.
5. A fall in the concentration of the serum inorganic phosphorus, beginning by the 6th day and reaching a minimum by the 18th day of treatment.
6. A gradual, progressive increase in the excretion of urinary calcium and phosphorus following calciferol therapy with a corresponding decrease in fecal calcium and phosphorus.
7. A progressive decrease in parathyroid symptoms corresponding with the rise in serum calcium and the fall in serum inorganic phosphorus which followed the administration of calciferol.

Control Subject. R. P., a white male, aged 42, had been under observation and treatment in the neurological division since September, 1935, suffering from myotonia atrophica. The patient was totally blind as the result of an accident many years before. His treatment had consisted of prostigmine, ephedrine, amphetamine, and more recently, glycine. The history and findings presented nothing to suggest abnormality of calcium or phosphorus metabolism. The important physical findings included absence of both eyes, muscular atrophy involving the neck and upper extremities, myotonia, and diminution or absence of tendon reflexes. The concentrations of calcium and inorganic phosphorus in the serum on admission were 10.3 and 4.2 mg. per 100 ml., respectively. The patient was under observation in the hospital from June 5, 1940, to July 6, 1940. During this time he was constantly maintained on a low calcium diet as indicated previously. The concentrations of calcium, inorganic phosphorus and protein in the serum were determined at the beginning of the period of study and

fication of the cranial vault. There was no evidence of decalcification of the long bones, spine or pelvis at this time.

It is also of interest that in Cases 1 and 2, the withdrawal of dihydrotachysterol was followed by a much slower return of serum calcium and inorganic phosphorus to their parathyreoprival levels and by a slower reappearance of parathyreoprival symptoms than was observed on other occasions following the withdrawal of calcium therapy. This suggests the possibility that dihydrotachysterol may be stored in the body. All 3 subjects remained in negative calcium balance. The 2 parathyreoprivic patients showed a positive phosphorus balance, whereas the "normal" control subject remained in approximate phosphorus equilibrium. Changes in organic urinary phosphorus excretion in the "normal" subject (J. P.) were not of such a character as to permit conclusions regarding their significance. The concentrations of serum protein in the parathyreoprivic individuals remained essentially unchanged, excepting that in Patient J. J. there was a fall of 1.1 gm. in serum protein coincident with the initial decrease in serum calcium.

Despite much speculation and the development of several theories, the actual mechanism whereby the parathyroid hormone regulates calcium and phosphorus metabolism remains in doubt. Likewise, the manner in which dihydrotachysterol and calciferol produce their characteristic effect upon the blood levels of calcium and phosphorus is not yet entirely clear. Three theories have been advanced to explain the primary action of the parathyroid hormone:

1. Albright and his group¹ suggest that the primary effect is upon the renal threshold for phosphorus and that the urinary excretion of phosphorus is the key factor in the regulation of calcium and phosphorus metabolism.

2. Thompson and Collip¹⁶ suggest that the parathyroid hormone acts directly to affect the delivery of calcium from the bones into the serum by stimulating osteoclastic activity. They point out that the characteristic effect of the parathyroid hormone upon osteoclastic activity can be produced despite total nephrectomy.

3. Shelling¹³ concludes that the parathyroid hormone controls the solubility of calcium and of inorganic, and possibly organic, phosphorus in the serum. In this connection, he points out that the serum is actually supersaturated with calcium and phosphorus and suggests that some humoral effect must be invoked to explain this apparent paradox.

The problem would appear to revolve largely around the reciprocal relationship between the concentration of calcium and inorganic phosphorus in the serum. The exact mechanism by which this relationship is maintained unfortunately still remains obscure.

Albright's explanation of the mode of action of calciferol has been referred to in our introductory paragraph. It should be noted that the observations of Tweedy and his co-workers¹⁸ tend to refute

5. A progressive decline in the urinary excretion of calcium before calciferol therapy. Following the administration of calciferol there was a gradual rise in urinary calcium excretion with a corresponding decrease in fecal calcium concentration.

6. A gradual, progressive increase in the urinary excretion of both total and inorganic phosphorus after the beginning of calciferol with a corresponding decrease in the concentration of fecal phosphorus.

The observations noted in this subject are in general similar to those reported by Bauer, Marble and Claflin⁵ in normal subjects (see above) with two exceptions: First, we did not observe the initial temporary increase in the fecal excretion of calcium and phosphorus which they noted immediately after beginning vitamin D; and second, the changes occurred in our patient with much smaller doses of vitamin D than those required to produce similar changes in their subjects.

Comment. The observations reported in Cases 1 and 2 confirm previous reports concerning the effectiveness of large doses of calciferol in the treatment of chronic parathyroid insufficiency.^{8,9,11} Our results, however, do not confirm the opinion of Klatskin⁸ that an adequate intake of calcium is necessary for the effective action of calciferol. The finding in Cases 1 and 2 of a negative calcium balance before the institution of therapy is not in agreement with the statement attributed to Aub and his co-workers by Anderson and Lyall³ that patients with parathyroid insufficiency remain in calcium equilibrium despite a calcium intake as low as 100 mg. a day. The changes, both absolute and proportional, in the urinary and fecal excretion of a calcium and phosphorus following calciferol therapy in Cases 1 and 2 are in general similar to those reported by Albright and his associates.²

The chief interest in our observations on the 2 patients with parathyroid insufficiency attaches to the fact that neither a normal calcium intake nor an "optimal" calcium:phosphorus ratio in the diet was necessary for the characteristic effect of calciferol upon calcium and phosphorus metabolism and the concentration of these substances in the serum.* It would appear inevitable that the prolonged maintenance of a negative calcium balance would result in exhaustion of body stores of calcium and in decalcification of the bones. Our observations were not continued over a sufficient period to ascertain whether such decalcification would occur. Patient J. J. (Case 1), however, showed no Roentgen ray evidence of decalcification of the bones, after she had been in negative calcium balance for 21 days. After she had taken 200,000 to 400,000 vitamin D units of calciferol daily for 15 months, with unrestricted diet, Roentgen rays of the skull showed some evidence of decalci-

* It will be noted that the calcium:phosphorus ratio in our patients' diets was approximately 1;4, and thus rachitogenic in type.

4. The 2 patients with hypoparathyroidism remained in positive phosphorus balance; the "normal" control subject was in approximate phosphorus equilibrium throughout.

5. The "normal" control subject developed no symptoms before or after the administration of calciferol. The changes in his serum calcium and inorganic phosphorus following calciferol were slight but qualitatively similar to those observed in the parathyreoprivic subjects.

Conclusions. 1. Patients suffering from chronic hypoparathyroidism may show a negative calcium balance, when the calcium intake and the calcium:phosphorus ratio in the diet are low.

2. Large doses of calciferol (vitamin D₂) are effective in relieving the symptoms of parathyroid deficiency and in restoring the serum concentrations of calcium and inorganic phosphorus to normal levels.

3. Neither a normal calcium intake nor an "optimal" calcium:phosphorus ratio in the diet is necessary for the effective action of large doses of calciferol.

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FURTHER EXPERIENCE WITH THE USE OF GUANIDINE HYDROCHLORIDE IN THE TREATMENT OF MYASTHENIA GRAVIS.

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IN 1938^{3a} and 1939^{3b} we reported the use of guanidine in the treatment of myasthenia gravis. Viets and Schwab⁷ also reported in 1939

this theory. These workers were able to obtain the characteristic effects of calciferol upon serum calcium in nephrectomized rats and concluded that the primary action of calciferol was to decrease the intestinal excretion of calcium. It is possible, however, that nephrectomy may alter the usual mechanism by which calciferol acts.

The increase in the concentration of serum calcium which occurred in our patients could have resulted from one or more of the following causes:

1. (a) An increase in the absorption of calcium from the intestine;
(b) a decrease in the excretion of calcium from the circulation into the intestine.
2. Increased delivery of calcium into the serum from body stores (*i. e.*, the skeleton).

The greatest increase noted in the concentration of serum calcium in any of our patients was 4.2 mg. per 100 ml. of serum which would indicate a total increase of approximately 100 mg. of calcium in the circulating serum. Furthermore, this increase occurred over a period of 18 days. Our data do not permit comment upon the possible mechanisms involved in producing the changes observed in the concentrations of serum calcium, since gain or loss of such amounts of calcium over a period of 18 days cannot be detected by current methods of balance studies.

Summary. Observations on calcium and phosphorus metabolism have been made upon 3 subjects (2 with chronic hypoparathyroidism and 1 control with myotonia atrophica without evidence of parathyroid disease). These observations were made before and during the daily administration of 400,000 units of vitamin D₂ (calciferol). Throughout the period of study the subjects were maintained upon diets low in calcium and containing slightly less than average normal amounts of phosphorus. The calcium and phosphorus contents of urine and feces were determined throughout the period of study and periodic determinations of the serum concentrations of calcium, inorganic phosphorus, and protein were made. The urinary excretion of organic phosphorus was likewise determined in the subject without parathyroid disease.

The results of our observations may be summarized as follows:

1. In the patients with hypoparathyroidism, serum calcium and inorganic phosphorus gradually returned to normal levels following the administration of calciferol. There was concomitant disappearance of parathyreoprival symptoms.
2. The urinary excretion of calcium and phosphorus increased following the administration of calciferol in all 3 subjects. This increase occurred at the expense of the fecal excretion of calcium and phosphorus.
3. All 3 subjects remained in negative calcium balance throughout (*i. e.*, the estimated excretion of calcium was greater than the estimated calcium intake).

soon gastro-intestinal symptoms developed. Subsequently, under the direction of various physicians different combinations of the two drugs have been tried with only partial success. In a recent letter he states that he is now taking 7 guanidine and 10 prostigmin tablets every 24 hours and that this "holds him on a fairly even keel." In this individual prostigmin and guanidine seems to cause gastro-intestinal symptoms easily. Tincture of belladonna, 10 minims 3 times a day, relieves the gastro-intestinal distress. It seems possible that a different combination of the 2 drugs or a change in the interval of dosage might result in a sustained response and eliminate the gastro-intestinal symptoms without the use of atropine.

Vanderbilt's Cases. Follow-up on Old Cases. *M. O., Case 2 of Original Paper.* A 37-year-old woman with myasthenia gravis of more than 5 years' duration had been maintained fairly satisfactorily on prostigmin. In January, 1938, she was started on guanidine medication. The dose was increased gradually (in the light of later experience needlessly slowly) to 30 to 35 mg. per kilo of body weight daily. At the end of 15 months she felt well, could do light housework and take automobile rides, but could not walk far because her knees tired easily. She continued the rather high daily dose of guanidine for several months at which time she found that satisfactory strength could be maintained with smaller amounts. At present she is taking 1.25 gm. of guanidine, or about 18 mg. per kilo, daily, in divided doses and supplements this with 2 or 3 15-mg. tablets of prostigmin. At no time has she experienced untoward symptoms from the long continued use of guanidine. The weakness of her knees has disappeared. She does her own housework and leads a normal social life. She was able to work as a clerk in her husband's hardware store for half of each day during the Christmas rush. She has no periods of marked weakness at any time and no undue fatigue at the end of the day. On a recent physical examination no abnormalities were found. The urine was normal, the blood pressure 120/80 and muscle tone excellent. Although this patient exhibits no evidence of myasthenia gravis while under appropriate medication, she is not in a spontaneous remission because symptoms of weakness recur if treatment is withheld.

H. W. C., Case 3 of Original Paper. A 47-year-old woman who had myasthenia gravis had, for economic reasons, taken inadequate amounts of prostigmin for several years. In May, 1938, guanidine medication was started. She was soon taking 20 to 25 mg. per kilo of body weight per day. During the first year of medication she was able to do more work than she had done for some years, but still tired easily. At about this time she experienced considerable discomfort, associated with symptoms typical of the menopause. She felt unable to undertake anything which required much muscular exertion. However, she could paint or sew for several hours without fatigue, there was no tiring of her voice in conversation, and her facial expression was normal and animated. Now, nearly 3 years since the beginning of guanidine treatment, she is in much better general health and is able to be considerably more active. She does her own housework, takes short walks and joins in more social activity than formerly. She has continued to require 20 mg. of guanidine hydrochloride per kilo per day. Weakness rapidly returns with the omission of a dose or two. She takes prostigmin occasionally during automobile trips or before some social function. She has been examined several times by her physician during the past year. Her blood pressure which for several years had been 170 to 200 over 110 to 120 has fallen since the menopause to 140 to 150/90. Although careful attention to medication continues to be necessary this woman now leads a nearly normal life. She states that she feels better than at any time since she developed myasthenia.

that they had given guanidine alone or with prostigmin to 25 patients with myasthenia gravis and had obtained some beneficial responses in one-third of the cases and good results in 4. In our second paper we were able to give the results of treatment of 5 patients, one of whom had taken the drug for a little over a year. We have continued to follow 3 of our original patients and have had an opportunity to treat 3 new patients with guanidine. Following our second report we received letters from several physicians who wished to know in greater detail how to use guanidine. In the autumn of 1940 we wrote to these physicians asking for a statement of their experience with the drug and received reports on the results in 21 cases. We have also heard from members of the pediatric staff of the Johns Hopkins Hospital concerning the use of guanidine in children. The purpose of this paper is to review the subject of guanidine treatment in myasthenia gravis in the light of accumulated experience.

Vanderbilt's New Cases of Myasthenia Gravis. CASE 1.—A 54-year-old woman, who weighed 141 pounds, developed difficulty with speech, swallowing and vision 5 years before admission to the hospital. A spontaneous remission of symptoms occurred but this was followed by a relapse. A diagnosis of myasthenia gravis was made and prostigmin and ephedrin prescribed. She returned 2 years later greatly improved. She was again in a remission but had difficulty in talking and eating and toward evening became very weak without medication. Ergographic tracings showed definite improvement in muscle strength following the ingestion of a single dose of 10 mg. of guanidine hydrochloride per kilo of body weight. There was a less pronounced and less well sustained response to 0.5 mg. of prostigmin injected hypodermically. She was given 250 mg. of guanidine a day and later her dose was increased to 500 mg. Ephedrin and prostigmin were discontinued. A recent letter states that she experiences no difficulty in speaking or swallowing and does not feel tired at the end of the day. She feels much stronger when taking guanidine and wishes to continue using it.

CASE 2.—A 72-year-old man developed generalized weakness 4 years ago. Five months before admission he found that he had to hold his eyelids up with his fingers in order to see. Two months before admission he developed difficulty in swallowing. He had stayed in bed for several months. Prostigmin, 5 to 6 tablets a day, brought about marked improvement. The patient had advanced arteriosclerosis and was greatly depressed by his own illness and the hopeless condition of his wife's health. He was very uncooperative so that it was hard to evaluate the results of medication. Nevertheless, he was obviously much stronger when he took 325 mg. of guanidine hydrochloride and 3 15-mg. tablets of prostigmin daily. Shortly after he left the hospital his wife died and he committed suicide.

CASE 3.—A 58-year-old naval officer¹ developed typical myasthenia gravis 2 years before admission to the hospital. He had ptosis of the upper lids, difficulty in breathing, talking, swallowing and later in walking. He was treated with prostigmin. On several occasions when his supply of prostigmin was limited he almost suffocated. In December, 1939, he began to take guanidine hydrochloride, 250 mg. 5 times a day, together with 6 tablets of prostigmin. He still had trouble eating his breakfast and at times could not speak clearly. In September, 1940, he came to this hospital where his dose was changed to 12 guanidine tablets of 125 mg. each and 10 15-mg. tablets of prostigmin. He responded excellently for a while but

admission and later drooping of the lids, slowed speech and difficulty in chewing and swallowing. Definite improvement in muscular strength followed the administration of prostigmin. She was given guanidine. The doses were gradually increased up to 10 mg. per kilo per day. Her strength increased and speech and swallowing improved. She had a spontaneous remission during which she required no medication. In a later relapse guanidine again produced improvement. When she was tried without medication or when placebos were substituted for guanidine, she became too weak to do anything actively. At present guanidine has been adopted as the most satisfactory therapy. On an amount somewhat greater than the original 10 mg. per kilo of body weight she is able to carry on the activities of a normal child. It seems possible that the other 3 children in whom weakness was localized suffered from some other form of muscular weakness than that usually diagnosed myasthenia gravis.

Discussion. Experience has reëmphasized the need for individualization in determining both the total daily dose and the appropriate spacing of doses for a given person. Diabetics and myasthenics are alike in that once the proper program of medication is established frequent modifications are unnecessary. Some myasthenics are very weak in the morning and need a large fraction of their total medication early in the day; others go through the day fairly well and need their greatest "lift" in the evening. Some can take the daily ration of guanidine subdivided into as few as 3 doses with evenly sustained strength and no gastric distress. Others do much better with a greater subdivision of the total amount. In our experience, it requires about 10 days of close observation to work out a satisfactory therapeutic schedule. Once this is accomplished the patient may be allowed to follow the plan independently with reasonable assurance that there will be no sudden change, either in drug requirement or tolerance. Either periods of weakness or gastro-intestinal unrest constitute signals that further adjustment of the treatment schedule is necessary. Two of the 3 patients we have treated for long periods require less guanidine now than at the beginning of treatment. The indication for decreasing their dosage was the appearance of mild gastro-intestinal symptoms and nervousness. We found that the dose could then be decreased to a level which no longer caused toxic symptoms without forfeiting the improvement in muscle function.

As we observe and compare the actions of guanidine and prostigmin in our patients it appears that guanidine gives a more sustained response. It perhaps never produces quite the feeling of well-being experienced at the height of prostigmin reaction and is never followed by the sensation of sudden "let down" as the effect wears off. Given their choice, our patients all prefer guanidine with its constant, steady effect, with prostigmin as a "cocktail" before an occasional social function, or some unusual activity.

We have no satisfactory explanation for the increased tolerance for guanidine exhibited by patients with myasthenia gravis. We

W. M. G., Case 5 of Original Paper. A 32-year-old woman who had had myasthenia gravis for over a year entered the hospital in August, 1938, in a relapse. In spite of prostigmin medication there were frequent periods during the day when she was unable even to swallow her saliva. She was started on guanidine medication, supplemented shortly with potassium citrate. Her required dosage was 40 to 45 mg. of guanidine per kilo of body weight. She was discharged markedly improved and by October was up and about the house most of the time. She did not feel extremely weak at any time in the 24 hours. She continued for 6 months to take the same large amount of guanidine hydrochloride, usually supplemented with 8 cc. of 25% potassium citrate 3 times a day. At the end of this period she complained of diarrhea, intestinal cramping and nervousness. The daily ration of guanidine was decreased without impairment of muscle function. The undesirable symptoms disappeared. During the last year 20 to 25 mg. of guanidine per kilo per day, intermittently supplemented with potassium citrate, has proved to be satisfactory therapy. She married a few months ago and leads a normal active life. A recent physical examination revealed no abnormalities attributable to her myasthenia or her medication.

Other Physicians' Cases. We have received reports of the treatment of 21 cases of myasthenia gravis in which sufficient details were given so that one could form some judgment of the value of guanidine therapy. In every instance myasthenic symptoms were improved. In 4 cases guanidine was considered markedly beneficial. One man has taken guanidine for 5 months. If he omits the drug for 24 hours he cannot chew or swallow or get about. With daily medication he has no trouble. Three patients in England, all of whom were doing fairly well with prostigmin alone, now take 500 mg. of guanidine 3 to 4 times a day together with prostigmin. Their physician* feels that these patients are better on the combination of guanidine and prostigmin than on either drug alone, but that the response to guanidine is more sustained than that to prostigmin. One of his patients has had a rash for 3 months but is so pleased with the way she feels when taking guanidine that she is unwilling to omit it even for a few days in order to find out whether the drug is responsible for the rash. A fifth patient from California⁶ survived a severe relapse in which prostigmin alone was ineffectual. Supplementary guanidine was administered intravenously in doses which on some days exceeded 1800 mg. In a subsequent relapse massive doses of guanidine together with frequent injections of prostigmin were not effective and the patient died. The other 16 patients in the group all responded to guanidine with an increase in muscle strength but for one reason or another were not maintained on the drug or were not followed by their physicians. Three of them died of myasthenia or from some other cause; several were lost sight of; one could no longer obtain the drug because of high customs duties; and 3 discontinued medication because of nausea and vomiting or other unpleasant symptoms. In at least 2 of the latter patients the guanidine dosage seemed to us to be poorly spaced, too large an amount being given at one time. Such a small group of case reports, in most of which the data are rather meager, does not lend itself to a satisfactory evaluation of guanidine in the treatment of myasthenia. Nevertheless, we are impressed by the following facts: in no instance did the patients fail to obtain symptomatic relief and 4 patients responded admirably to guanidine treatment.

At the Johns Hopkins Hospital⁸ 4 children on whom a diagnosis of myasthenia gravis has been made have been treated with guanidine. The first 3 patients have weakness of the muscles of the face, eyes, mouth and pharynx only. The weakness is remittent. For them guanidine is ineffectual. The fourth patient had easy fatigue and weakness for 4 months before

* Personal communication.

PRIMARY CARCINOMA OF THE LIVER IN HEMOCHROMATOSIS.

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THE association of primary carcinoma of the liver with hemochromatosis has been commented on by several authors.^{1, 9, 13, 14, 17, 24-26, 28a, 31} Little thought is given to them in clinical practice because both conditions are uncommon and the two together quite rare. In the vast majority of instances the diagnosis of either disease is first made only at the time of surgical exploration or at necropsy. In not a single instance, to the best of our knowledge, has a correct preoperative or premortem diagnosis been made when both were coëxistent. It is our purpose in this communication to emphasize the frequency with which these morbid processes tend to be associated and to call attention to several features which, if duly considered, may lead to a diagnosis of their coëxistence.

Incidence of Primary Carcinoma of the Liver in Hemochromatosis. From Jan. 1, 1920, to Dec. 31, 1940, autopsies were performed at the Jefferson Hospital on 3 cases of hemochromatosis, 2 of which had, in addition, a primary carcinoma of the liver. Autopsies on 12 cases of hemochromatosis were performed at the Philadelphia General Hospital between Jan. 1, 1920, and Dec. 31, 1939. Only one of these was associated with a primary carcinoma of the liver. At these two institutions, therefore, out of 15 cases of hemochromatosis (11 males, 4 females) encountered in the course of routine postmortem examinations 3 (20%), were complicated by a primary hepatic malignancy. In Table 1 has been tabulated several reports which together survey the subject up to 1938. To them our own figures have been added. The average of these establishes the incidence of primary carcinoma of the liver in hemochromatosis as 7.3%.

Advanced portal cirrhosis is almost invariably a feature in the liver in hemochromatosis. Evidence of such a cirrhosis was present in every case in our group. There are two contending views as to the incidence of primary carcinoma of the liver in hemochromatosis. Several authors state that the incidence is no greater than that in uncomplicated portal cirrhosis,^{25, 26, 28a, 31} while others believe that there is an increased incidence due to the added factor of pigmentation.^{1, 17, 22} Of a total of 950 cases of cirrhosis of the liver of all types and grades occurring at the Jefferson and Philadelphia General

have shown² that myasthenic patients do not excrete unchanged any greater proportion of administered guanidine than do normal individuals. Neither do they tolerate without symptoms a persistently higher level of guanidine in the blood than do normal people. Whether their ability to ingest and retain guanidine is due to more rapid transformation of the drug to some non-toxic compound or to an ability to store it unchanged in tissue cells are questions which remain unanswered.

The mechanism through which guanidine exerts its effect on muscle function in myasthenia gravis is not known. Neither is the essential mechanism responsible for the effectiveness of prostigmin completely understood. The duration of the improvement of muscle function following a dose of prostigmin coincides with the time during which the activity of serum choline esterase is markedly depressed by the drug. The presumption is often made that there is a causal relationship between the depression of esterase activity and improved function. The effect of guanidine hydrochloride on choline esterase activity has been studied.¹ No inhibitory effect was demonstrated even with much higher concentrations of guanidine than can be maintained in the living animal organism. Recent studies by Osterhout,⁵ working with simple forms, demonstrated that guanidine restores the potassium effect and irritability to cells of *Nitella* after these properties have been lost by leaching the cells in distilled water. More extensive studies of this nature probably offer the greatest hope of an ultimate explanation of the mechanism responsible for the dysfunction in myasthenia gravis and for the therapeutic action of various drugs.

Conclusions. Guanidine hydrochloride causes temporary improvement in muscle function in most patients with myasthenia gravis. Myasthenics have an increased tolerance to guanidine. Prolonged medication produces sustained improvement in muscle function without harmful effects. As a rule, less of the drug is required after several months of adequate medication. Individual attention is necessary to establish a proper schedule of medication but frequent readjustment of the guanidine ration is thereafter unnecessary. Guanidine, unlike prostigmin, does not inhibit the activity of choline esterase. It may play a fundamental rôle in restoring irritability to cells.

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associated cirrhosis. Table 3 is a tabulation of a series of similar reports, including our own. The average of these indicates that cirrhosis is present in but 61.3% of all cases of primary hepatic carcinoma.^{10,11,15,21} It appears, therefore, that some factors in addition to the cirrhosis must be instrumental in the production of malignant transformation of the liver in hemochromatosis.

Diagnosis of Primary Carcinoma of the Liver in Hemochromatosis. Diagnosis is difficult when both primary carcinoma of the liver and hemochromatosis are coëxistent because many of the clinical manifestations of each are common to both. Several features, however, are far more common to primary carcinoma of the liver than to uncomplicated hemochromatosis and in their presence the clinical suspicion of coëxistent disease is warranted.

Duration of Symptoms. Hemochromatosis is notoriously a chronic disease of long standing.^{5,12,25} It has been estimated that in order to account for the amount of iron retained, the onset of the disease must be dated back 30 to 50 years from the time a diagnosis is made. In 89 instances the average period that elapsed between the first calling of medical advice and death was 18½ months.²⁶ The shortness of this period was due to the large proportion of cases dying from diabetic coma in pre-insulin days, and there is now indication that it will be considerably lengthened through the use of insulin.^{5,18}

Patients with primary carcinoma of the liver, on the other hand, rarely live more than 4 months after the onset of symptoms,^{3,13,14,27,30} even when the malignancy is found in association with hemochromatosis.^{25b}

Whenever, therefore, a known or suspected case of hemochromatosis presents a symptom complex of short duration and rapid progression a complicating hepatic cancer should be suspected.

Abdominal Pain. Subjective abdominal symptoms in hemochromatosis are rare.²⁶ Abdominal pain is the commonest of these yet, excluding those with complicating carcinoma of the liver, pain was present in only 21 of the 311 cases reviewed by Sheldon.²⁶ Of our 12 patients with hemochromatosis uncomplicated by malignancy pain was described by 3, and in 2 of these it was preagonal.

Abdominal pain in patients with carcinoma of the liver is a prominent feature^{13,14,27} (29%¹³). In all 3 of our patients with both hemochromatosis and carcinoma of the liver, pain was present and was an outstanding complaint.

The presence, then, of abdominal pain in a known or suspected case of hemochromatosis should arouse the suspicion that a malignant change may have occurred in the liver.

Jaundice. In typical uncomplicated hemochromatosis, jaundice is rare.^{1,25} Sheldon²⁶ found it mentioned only 7 times in 311 cases. Butt and Wilder⁵ failed to find it in any of their 30 cases. It was noted, however, in 3 of our 12 patients with uncomplicated hemochromatosis.

Hospitals, 32 (3.4%) were complicated by the development of primary carcinoma of the liver (Table 2). This incidence is to be compared with that of 20% of hepatic cancer in cases of hemochromatosis at the same institutions (Table 1).

TABLE 1.—INCIDENCE OF PRIMARY CARCINOMA OF THE LIVER IN HEMOCHROMATOSIS.

Author.	Year.	No. of cases of hemo-chromatosis.	No. with primary carcinoma of liver.	% primary carcinoma of liver in hemo-chromatosis.
Stewart ^{28b}	1931	52	6	11.5
Sheldon ²⁸	1935	345	20	5.8
Wellenweber, Binford and Laurence ³¹	1938	24	3	12.5
Berk and Lieber	1941	15	3	20.0
Average		436	32	7.3

TABLE 2.—INCIDENCE OF PRIMARY CARCINOMA OF LIVER IN HEPATIC CIRRHOSIS.

Author.	Year.	No. of cases of cirrhosis.	No. with primary carcinoma of liver.	% primary carcinoma of liver in hepatic cirrhosis.
Blumenau ²	1921	198	7	3.5
Stewart ^{28a}	1922	149	4	2.8
Ophüls ²³	1926	128	8	6.2
Counsellor and McIndoe ³	1926	127	5	3.9
Stewart ^{28b}	1931	264	9	3.4
Rosenthal ²⁵	1932	68	7	10.3
Lynch ²⁰	1937	11	6	54.5
Loesch ¹⁹	1939	94	12	12.7
Berk and Lieber	1941	950	32	3.4
Average		1989	90	4.5

A series of reports on the incidence of primary hepatic carcinoma in cirrhosis of the liver to which our own has been added is tabulated in Table 2. The average of these is 4.5%, which is in contrast with the average of 7.3% for the same complication in hemochromatosis (Table 1).

TABLE 3.—INCIDENCE OF CIRRHOSIS IN PRIMARY CARCINOMA OF LIVER.

Author.	Year.	No. of cases primary carcinoma of liver.	No. with cirrhosis.	% cirrhosis in carcinoma of liver.
Stewart ^{28b}	1931	295	244	82.7
Tull ³⁰	1932	134	98	73.1
Strong and Pitts ²⁹	1932	12	11	91.6
Brines ⁴	1933	11	2	18.1
Smith ²⁷	1933	25	9	36.0
Boyce and McFetridge ³	1934	28	12	42.8
Lynch ²⁰	1937	6	6	100.0
Collenberg ⁷	1937	18	11	61.1
Gustafson ¹⁴	1937	62	32	51.6
Loesch ¹⁹	1939	14	12	85.7
Greene ¹³	1939	386	(189)	49.0
Berk and Lieber	1941	82	32	39.0
Average		1073	658	61.3

Further perusal of our records showed a total of 82 cases of primary carcinoma of the liver in only 32 (39%) of which there was an

weight in 11 such cases collected by Stewart^{28b} was 3369 gm. and in the 2 of our 3 cases in which it was noted the liver weighed 2000 and 2570 gm. respectively. In consistency, the carcinomatous liver is stony-hard and its surface is frequently irregular and grossly nodular. In further contradistinction to the uncomplicated hemochromatotic liver, whenever there is a disproportionate enlargement, as by a massive solitary growth, the right lobe is more often affected than the left.

The presence, hence, of a liver which is massive in size, particularly if it extends upward, and which is extremely hard in consistency and grossly nodular in character or whose right lobe is disproportionately enlarged, suggests carcinomatous involvement of that liver in an individual known or suspected to have hemochromatosis.

Diabetes Mellitus. An impairment in carbohydrate metabolism is one of the cardinal features of hemochromatosis. Diabetes mellitus has been reported in 86.6%⁵ and glycosuria in 78%.²⁶ A marked instability of carbohydrate metabolism is characteristic of many of these individuals and in some it is manifested by an undue liability to hypoglycemic shock, particularly following the use of insulin.²⁶

It is well known that in instances of previously existent diabetes mellitus, any damage to the liver, as from neoplastic infiltration, will not uncommonly cause a sudden amelioration of the severity of the diabetes. Recurrent hypoglycemia has been described in several cases of primary hepatic malignancy.¹³

A suspect or proven hemochromatotic with established diabetes mellitus, who displays a sudden amelioration of the diabetes and a liability to hypoglycemic intervals, should be viewed from the standpoint of possible neoplastic change in the liver.

Fever.—No mention is made of fever in uncomplicated cases of hemochromatosis, so that it may be assumed that fever is either not seen or very unusual.

Primary carcinoma of the liver, in contradistinction, is often associated with fever (14% to 47%).^{10,14,27,30}

A persistent otherwise unexplained fever in a patient with known or suspected hemochromatosis requires that the possibility of cancer of the liver be considered.

Anemia. The red blood cell count and the hemoglobin concentration in hemochromatosis are practically within normal limits and the disease is not characterized by an anemia.²⁶

Primary carcinoma of the liver, on the other hand, is accompanied by an anemia in the majority of instances.^{13,14,27}

The presence of an anemia, therefore, in a known or suspected hemochromatotic is suggestive evidence of possible hepatic cancer.

Leukocytosis. The white blood cell count and the differential count in hemochromatosis is essentially normal (average 7030 per c.mm.).²⁶

More than half of all patients with primary carcinoma of the liver display jaundice at some time or other (34 to 72%^{1,10,14,27,30} with an average of about 52%¹³). Two of our 3 patients with both hemochromatosis and hepatic malignancy were jaundiced, while Stewart^{28b} noted it in 37.5% of 16 similar patients.

Clinical jaundice in a known or suspected case of hemochromatosis is another finding which should arouse suspicion of malignant transformation in the liver.

Ascites. Ascites is not uncommon in hemochromatosis, being seen in 10%⁵ to 22%²⁶ of all cases. It was noted in 2 of our 12 uncomplicated cases. Characteristically, however, it occurs as a terminal event. It is unusual for it to require frequently repeated paracenteses. In the absence of complications, the fluid is a clear yellow transudate.

The incidence of ascites in primary carcinoma of the liver, by comparison, is much greater (45% to 80%^{10,14,27,30}, with an average of about 66%¹³), even when the carcinoma is associated with hemochromatosis (all 3 of our cases and 80% of Stewart's^{28b} 15 cases). Since the disease is one of short duration, it also appears in what may be called the terminal phase. Because of the widespread carcinomatous plugging of the intrahepatic branches of the portal vein the ascites tends to reaccumulate rapidly. In a considerable percentage, also, the fluid is grossly bloody or serosanguineous.

An ascitic collection which requires frequent and repeated paracenteses and which is sanguineous in character would justify a presumptive diagnosis of complicating hepatic malignancy in a known or suspected case of hemochromatosis.

Condition of the Liver. Enlargement of the liver occurs so regularly in hemochromatosis (92%) that it is regarded as the most constant clinical feature of the disease.²⁶ Although it is usually considerable, the extent of the enlargement is variable. The weight of the liver in our 12 uncomplicated cases varied from 1200 to 3170 gm., with an average of 2019 gm. In 6 (50%) it was said to be enlarged clinically. The organ feels harder than normal, but is not rock-hard. It is almost always smooth, though occasionally a fine nodularity can be felt. In some cases the left lobe appears to be particularly enlarged, a finding that is claimed to be characteristic of uncomplicated hemochromatosis.¹

The liver which is the site of a primary carcinoma is likewise clinically enlarged in a great percentage of cases (70% to 84%^{14,27}. Characteristically, however, the liver tends to extend upward^{13,29,30} so that the frequency with which it can be palpated (48%¹³) is a poor index of its enlargement. As a rule the actual increase in size is great, the average weight in one series being 3366 gm.²⁷ and in another 2950 gm.³⁰ Even when associated with hemochromatosis the carcinomatous liver is, on the average, a heavier and larger one than that found in uncomplicated hemochromatosis. The average

(4.5%) and is apparently due to other factors in addition to the cirrhosis of the liver found in hemochromatosis.

2. The coëxistence of a primary carcinoma of the liver in a known or suspected case of hemochromatosis is suggested whenever any or all of the following occur: a symptom complex of short duration and rapid progression; abdominal pain; jaundice; a rapidly recurring, sanguineous ascites; a markedly enlarged liver which extends upward and is extremely hard and grossly nodular; sudden amelioration of the diabetes and/or liability to hypoglycemic intervals; fever; anemia; leukocytosis; weight loss; evidence of metastatic involvement, especially of the lung.

3. Early diagnosis and prompt attempt at surgical removal of the neoplastic process is the only procedure of any avail.

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WATER METABOLISM IN PREGNANCY.

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EXISTENCE of a positive water balance in women during pregnancy has long been assumed. The increased turgidity of the skin, along with the frank edema noted with certain toxemias, provided such

The white blood cell count in primary hepatic cancer is variable but tends toward the high side (average 10,900¹⁴ with a range from 2800 to 44,000 cells per c.mm.¹³).

In the absence of a demonstrable septic complication, a marked leukocytosis in a known or suspected case of hemochromatosis would advance malignancy of the liver as one of the explanations.

Loss of Weight. Loss of weight in hemochromatosis is not uncommon, principally because of the frequency with which diabetes mellitus occurs. Loss of weight from non-diabetic causes is unusual.²⁶

As is generally true of neoplasia, primary carcinoma of the liver is often accompanied by loss of weight (41 %).¹³

Whenever a known or suspected hemochromatotic shows an exorbitant weight loss without corresponding evidence of an increase in the severity of the diabetes which may be associated, then thought must be given to the possibility of malignant transformation in the liver.

Metastases. The ability to demonstrate a neoplastic metastatic involvement is, of course, proof positive that a known or suspected hemochromatotic process is at least complicated by neoplasia. In view of the preponderance of primary malignancy of the liver in this disease, first thought must be given that organ as the primary site.^{28b} It must be remembered in this respect that primary carcinoma of the liver characteristically shows distant metastases much less frequently than does carcinoma elsewhere. The lungs and the regional lymph nodes are the most frequent sites of extrahepatic metastasis, the former being involved in from 18% to 28%.^{6,10,13,14,19}

Metastasis to the lungs, therefore, would support suspicion of the liver as the primary site but failure to demonstrate metastasis would not exclude primary neoplasm of the liver if other evidences suggested a complicating malignancy.

Comment. Detailed consideration of the features that might lead to a correct diagnosis of so rare a combination as primary carcinoma of the liver and hemochromatosis might appear commendable academically but useless practically. In fact, the attitude, generally adopted toward primary carcinoma of the liver, no matter with what it may be associated, is one of dismay and hopelessness. It is well to recall that the disease is amenable to surgical extirpation in some instances providing the diagnosis is correctly established without undue delay. Even the early attempts at operative correction yielded a surprisingly high percentage of recoveries¹⁶ and more recent efforts are achieving even greater successes.⁶ No matter how unusual the situation, an early diagnosis of primary carcinoma of the liver must be sought and its surgical removal considered as the only therapy of any avail.

Conclusions and Summary. 1. Primary carcinoma of the liver occurs with surprising frequency in hemochromatosis (7.3%). The incidence appears to be greater than in uncomplicated hepatic cirrhosis

sodium balance in the latter part of pregnancy and concluded from his careful study that after proper allowance was made for other allocations of water, no considerable maternal superhydration was found.

Plan of Study. These studies on water balance were conducted on 2 women. One of these (H. R.) served as subject over 10- and 11-day observation periods in the fourth and eighth months of pregnancy respectively. Her basal metabolic rate, in the first experiment was -17% , but she seemed normal in all other respects. The other subject (D. V.) had a blood pressure of 152/88, and slight ankle edema. Her urine contained a trace of albumin. On this second subject the study was terminated after 5 days, during which time complete data were obtained, because of the onset of labor at term.

On admission complete physical and laboratory examinations were done. During a preliminary 3-day period the subjects became accustomed to the rigid daily routine especially that relating to diet and elimination. After this, the actual determinations were begun. Nurses especially trained for this type of study were in almost constant attendance. Only simple bedroom diversions were permitted the subjects. The temperature, humidity, and restricted activity were of such character as to preclude visible perspiration, thereby reducing variables to a near minimum.

The daily diet in each experiment consisted of the following:

Distilled water	2500 gm.
Powdered whole milk	252 "
Lactose	36 "
Chocolate malted milk	20 "
Graham crackers	50 "
Tomato juice	400 "
Dextrin	20 "
Sucrose	10 "
Sodium chloride, 10% sol.	30 cc.

All the foods came from containers having the same lot numbers. Save for the Graham crackers, all food was pooled and given in fluid form from sealed refrigerated reservoirs holding sufficient quantities for the entire experiment. This diet provided, by analysis, approximately protein, 70 gm.; fat, 77 gm.; carbohydrates, 230 gm.; calcium, 2.17 gm.; phosphorus, 1.86 gm.; iron, 0.005 gm., and was calculated to yield 1948 calories. Since the measured diet consumption was precisely the same from day to day, the need for repeated analyses was obviated.

The study periods began and ended at 8 o'clock on consecutive mornings. At this hour, and after voiding, but before breakfast, the subjects were weighed to within 10 gm. Blood samples were then taken as needed. Quantitative meals and distilled water were given at regular intervals, *i. e.*, 8.30 A.M., 1.30 P.M., and 6 P.M. Care was taken that the entire diet, with rinsings from the dishes, was consumed at each meal. At the end of each experimental period, venipuncture was again performed after final weighing.

Collection of Excreta. The urine was passed directly into a receptacle packed in ice and containing 10 cc. of glacial acetic acid. Aliquots from the mixed 24-hour specimen were analyzed for sodium, potassium, and nitrogen. The stools were marked with carmine at the beginning and end of each experimental period, and stored in a vessel containing 10 cc. of glacial acetic acid and a measured quantity of distilled water. This mixture was subjected to thorough mechanical agitation and sampled for analysis. Since the stools were irregularly passed, the constituents were pro-rated on a daily basis.

apparently ample though crude evidence of water storage that more critical proof seemed superfluous. More subtle corroboration of this assumption was furnished by the observation of an inordinate gain in weight and, at times, of a diminished urinary output. De Lee⁴ has said that edema occurs in half of all pregnant women. And, if one adverts to the statement of Wiggers²¹ that a 10% increase in the fluid content of tissue is a prerequisite to its pitting, and to one of Gottlieb⁶ that large amounts, as much as 6000 cc., of edema fluid may be present in the body without visible evidence of edema, one can appreciate the almost syllogistic relationship which has been implied between pregnancy and water retention.

It might seem that measurement of water entering and leaving the body were an elementary arithmetical problem. Unsifted estimates which take cognizance only of water taken in as such and of the urine passed, ignore not insignificant quantities of water contained in solid foods such as meat, bread and potatoes. Furthermore, after many foods are metabolized their end-products leave the body largely as water. With fats, the water formed by oxidation may actually weigh more than the fats ingested. Such water should be regarded as intake. The insensible water loss from lungs and skin has also often been excluded from reckoning, as has been the moisture of the stools. Furthermore, a given volume of urine should not be regarded as representing an equivalent quantity of water. That this is true was rather convincingly demonstrated in one of the experiments herein described in which one subject eliminated over a period 7 times as many solids, by weight, in the urine as in the stools.

The understanding of water metabolism in pregnancy may transcend academic interest and become a matter of clinical importance, especially when treatment may depend on one of the current views held on the etiology of toxemia. In 1917 Zangemeister²³ proposed the idea that cerebral edema might cause eclampsia. This general concept is supported by Arnold and Fay,¹ who hold that water imbalance may produce symptoms not peculiar to eclampsia alone, but also to other disturbances caused by cerebral edema and increased intracranial pressure. Attention has been called to the similarity of eclamptic convulsions and those produced in animals by the forced administration of water. Failure of the body to eliminate excessive accumulation of water may produce such symptoms as muscle tremors, tonic and clonic convulsions, stupor, and death.²¹ Clinical studies by McQuarrie^{9,10} indicate that dehydration favors the cessation of epileptic seizures, while superhydration favors their recurrence. That symptoms of water intoxication are associated with disturbances in salt equilibrium and diminution in electrolyte concentration, was shown by Rowntree¹⁶ who noted that these symptoms are mitigated by adequate salt administration. More recently Freyberg⁵ described parallel shifts in body water and

Results. The data are presented in a series of figures which are largely self-explanatory. The amount of insensible water loss and the completeness of oxidation of foods was not ascertained. Actual total energy expenditure was not measured. Values assigned for water of oxidation and for vaporization, although they cannot be specifically applied, tell quite approximately what values may be assigned to these factors. Different methods of computation will accordingly give varying figures, which, for comparison, are graphically illustrated.

Data on a Typical Case. The first day of Experiment I (Subject H. R., 4 months' pregnant) may serve as a prototype. The diet contained 2500 gm. of distilled water. An additional 409 gm. of water were furnished by the moisture of the foods, largely from the tomato juice. Oxidation of the food provided another 250 gm. of water. The total water available for the day accordingly was 3159 gm. During this same 24-hour period the urine contained 2371 gm. of water. The pro-rated moisture content of the stools for that day was 81 gm. By applying the table of Benedict and Root, the expected insensible perspiration corresponding to a heat production of 1948 calories was assumed to be about 1128 gm. The balance between fluid intake and output can be summarized by Formula 1 as follows:

<i>A (Intake).</i>		<i>B (Output).</i>	
Water in diet . . .	2500 gm.	Water in urine . . .	2371 gm.
Moisture in food . . .	409 "	Water in stools . . .	81 "
Water of oxidation . . .	250 "	Insensible perspiration . . .	1128 "
<hr/>		<hr/>	
Total water available . . .	3159 "	Total water lost . . .	3580 "
Water apparently retained (A - B) = -421 gm.			

By applying Johnston's and Newburgh's estimate that evaporation of water from the skin and lungs will dissipate about 28% of the heat produced, the total output of water is calculated to equal 3392 gm., giving a balance of -233 gm.

Another method for calculating the insensible perspiration as suggested by Bassett and McQuarrie is noted by Formula 2 as follows:

<i>A (Intake).</i>		<i>B (Output).</i>	
1st wt. of subject . . .	53,280 gm.	2d wt. of subject . . .	53,210 gm.
Wt. of food and water . . .	3,320 "	Wt. of urine . . .	2,488 "
<hr/>		Wt. of stool . . .	116 "
56,600 "		<hr/>	
		55,814 "	

Insensible water loss (A-B) = 786. When this amount, 786 gm., is added to the water of the stools and urine (see Formula 1), the total water loss becomes 3238 gm. This amount, on subtraction from the total fluid intake of 3159 gm. accounts for a negative water balance of 79 gm. for the day.

Analytical Methods. Water content of the food, urine, and stools were determined by desiccation to constant weight. Nitrogen was determined by the Kjeldahl method. Protein was regarded as $N \times 6.25$. Analyses for carbohydrates and fat were not done by us, but their values were computed from data supplied by the manufacturers of the foods. Sodium and potassium were determined by methods described by the authors¹⁹ in a related experiment on electrolyte metabolism in pregnancy.

Available water was regarded in this study as coming from two sources: 1, water taken in as such, and contained as moisture in the foods; 2, water of oxidation. Newburgh and Johnston¹³ have suggested the "preformed water" as another source of water. Peters and Lavietes¹⁴ have, however, questioned the validity of the inclusion of this preformed water in the calculations, believing that there is little evidence that water is physically or chemically combined with protein, carbohydrates, or fat. The computations of water exchange here given are quantitative estimates based in part on analyses capable of accurate measurement and in part on indirect calculations. Some 60 gm. of water are liberated by oxidation of 100 gm. of carbohydrate, and 41 and 107 gm. of water become available from like amount of protein and fats respectively. An average mixed diet of some 3000 calories might then be expected to yield some 2000 cc. of actual water.²¹ Total water loss, in addition to the water in the urine and stools, includes that lost insensibly through the lungs and skin. Rather elaborate equipment is required to measure accurately and directly this latter fraction under the conditions of ordinary life. Soderstrom and Du Bois¹⁸ reported that if 0.584 calorie are required to vaporize 1 gm. of water at 22° to 24° C., about 24% of the total heat produced by the body is dissipated in the evaporation of water from the skin and lungs. These investigators found that few normal men varied more than 10% from this figure. Johnston and Newburgh⁷ give a slightly higher value, viz., 28%, as the fraction of heat lost from the body by vaporization. Benedict and Root³ have prepared tables showing such a close relationship between basal metabolism and basal insensible water loss that either one can be estimated from the other. Under certain conditions there is a high correlation between total weight change and the insensible water exchange. Thus, Manchester and associates¹¹ regarded the total insensible water loss for a period as representing the difference between body weight at the beginning of the period plus the weight of all ingesta, and the weight of the body at the end of the period plus the weight of the excreta. Bassett and coworkers² estimated the insensible loss of water by correcting the difference between items of intake and output for the net change in weight of the subject during 24 hours. Rockwell¹⁵ has also presented data illustrating the close correlation between water balance and changes in body weight when there are no complicating factors of food storage.

Newburgh and coworkers have given the following constants for determining oxygen absorbed and carbon dioxide given off in the oxidation of a diet:

<i>Oxygen.</i>		<i>Carbon Dioxide.</i>	
Multiply grams of protein	by 1.38	Multiply grams of protein	by 1.46
Multiply grams of fat	by 2.86	Multiply grams of fat	by 2.78
Multiply grams of carbohydrate	by 1.13	Multiply grams of carbohydrate	by 1.54

For Formula 3, the weight of oxygen absorbed in the oxidation of the diet (579 gm.) is added to the intake column, and the weight of the carbon dioxide liberated (674 gm.) is added to the output column of Formula 2. This method of calculation will give 691 gm., as the allotment for the insensible water loss, an amount so much less than that calculated by the previous methods that for this day the water balance is regarded as +16 gm.

Because of the close relationship between electrolyte and water metabolism, a consideration of either alone is incomplete. Wiley and associates²² have shown that sodium and potassium retention is accompanied by water retention. Tisdall²⁰ found that the bases, excluding calcium, and water leave the body in approximately the proportion in which they exist in the plasma, and has suggested the application of this relationship for the estimation of water exchange from the determination of base balance. Laviertes *et al.*⁸ has developed equations based on the thesis that base tends to distribute itself in the fluid media of the body in a fixed proportion to water. His equation is incorporated in Formula 4 in the present study and is as follows:

$$\Delta W = \frac{b + W_1 \times \Delta B}{B_2}$$

in which ΔW = water exchange

b = net gain or loss of Na + K by the body

W_1 = vol. of water in body at start of study period

ΔB = change in concentration of base in the water of the serum

B_2 = concentration of Na and K in the water of the serum at conclusion of study period

This formula in contradistinction to the other formulas was not used in computing daily retentions of water, but for the retentions over the entire period of study.

The net or accumulative water balances for the entire metabolic study period are shown in Table 1.

TABLE 1.—WATER BALANCE (Gm.).

	Form. 1.	Form. 2.	Form. 3.	Form. 4.	Nitrogen balance, gm.	Weight changes, gm.
Exp. I:	-3617.53	-350 20	+465 33	+1960	-4.96	-90
Exp. II:	-1580.10	-157.15	+813.77	+1590	+2 56	+180
Exp. III:	-759 80	-1526.90	-1053.25	+1200	-10 21	-570

It will be noted that wide but consistent diversities in results follow the application of the different formulas. In Experiment II

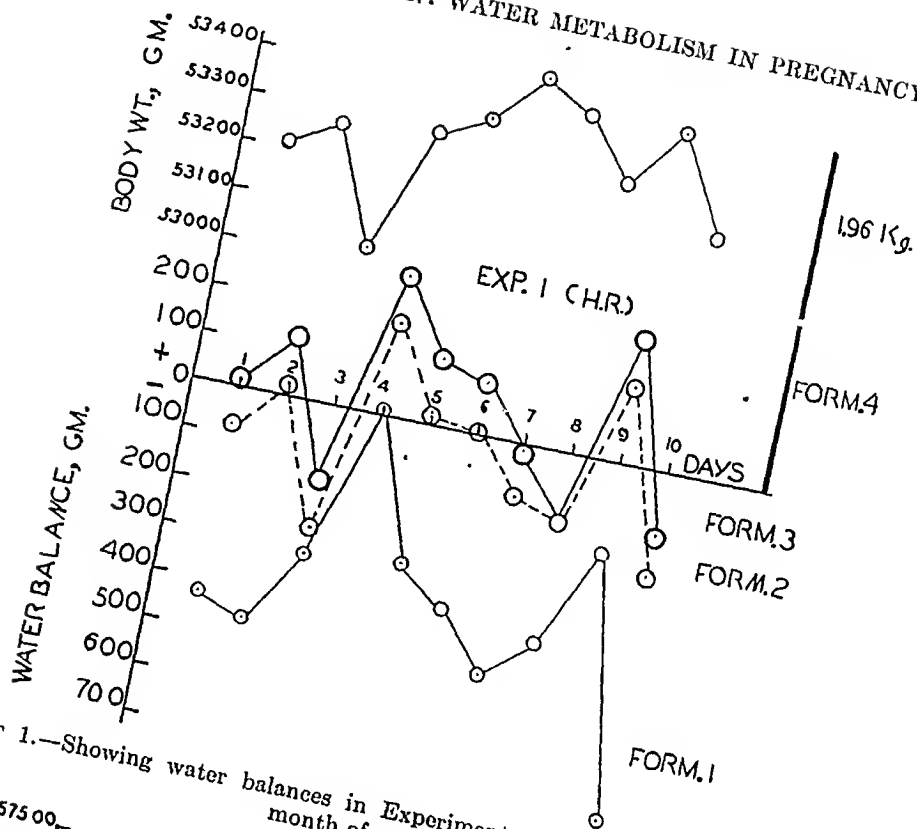


CHART 1.—Showing water balances in Experiment I. Subject H.R., in fourth month of pregnancy.

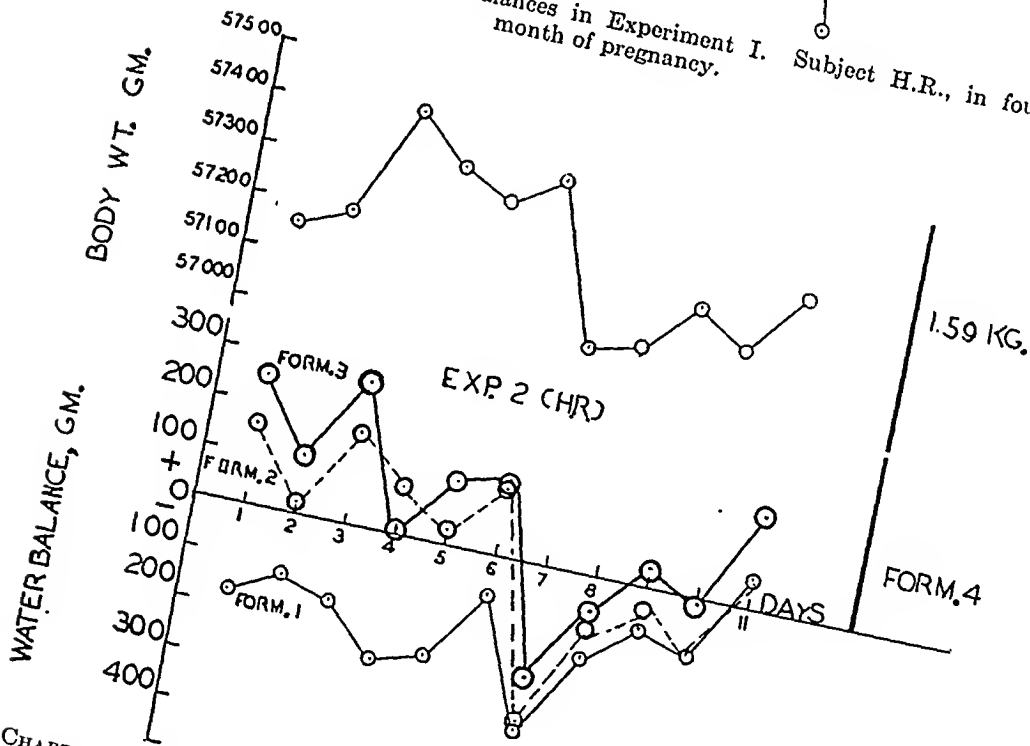


CHART 2.—Showing water balances in Experiment II. Subject H.R., in eighth month of pregnancy.

A change in the habits of the subjects from those associated with household duties to the sedentary life in the ward may have contributed to the results obtained. Certainly longer periods of observation would be desirable. Information concerning the influence of different levels of fluid, salt, nitrogen, and caloric intake on water retention is still limited. As yet unknown factors must modify the need for water storage. Marshall¹² has stated that physiologic variations in water content in man may vary as much as 2 kilos.

Subject H. R. received practically an identical diet in Experiments I and II. Yet during the eighth month of pregnancy, when she weighed some 4 kilos more than she did during the fourth month, she gained more in weight and nitrogen and, save for computations by Formula 4, also gained more in water. In Experiment III the subject had mild symptoms of toxemia with some edema at the beginning of the 5-day observation period, which ended when the patient went into labor. Extreme caution is necessary in drawing conclusions from this experiment. To what extent the weight loss of 570 gm. may have represented merely that which quite commonly precedes labor or that caused by the unloading of water caused by diarrhea is not known. When Formula 4, the formula which seeks to relate water balance to mineral balance and concentration is applied, it yields results quite out of proportion and in excess to those expected. It would seem unlikely that subjects losing 90 and 570 gm. in weight would be depositing 1960 and 1200 gm. of water respectively over the same period of time.

Summary. Credible clinical evidence of water storage in certain toxemias of pregnancy is supplied by edema and inordinate gain in weight. Water made available includes not only that taken as such or incorporated with food, but also that liberated by the various oxidation mechanisms within the body. Water loss in the stools and urine can be measured accurately, but the insensible loss from the skin and lungs, a very appreciable fraction of the total loss, is difficult to measure directly, but must be reckoned with. Under limited conditions this insensible water loss can be estimated from the weight loss, but allowance should be made for O_2 absorbed and CO_2 given off. A correlation between insensible water loss and the basal metabolism has been mentioned. Another method for estimating water balance rests on the thesis that bases and water leave the body in the approximate proportions in which they exist in the plasma.

Several formulas for the determination of water balance in 3 controlled experiments on 2 pregnant women have been applied. Even though each formula possesses a degree of merit, there is no constancy or trend among the results derived from the various formulas.

Conclusions as to water gain or water loss in these experiments are inconclusive and depend upon whatever formula is accepted.

the computed water balances range from -1580 to $+1590$ gm. During this period the subject gained 180 gm. in weight and deposited some 2.56 gm. of nitrogen. The disparity between weight changes and the calculated water balances for the metabolic periods hardly lends credence to the claim that a gain or loss of body weight necessarily corresponds closely to water balance. Obviously, other factors than those recorded come into play.

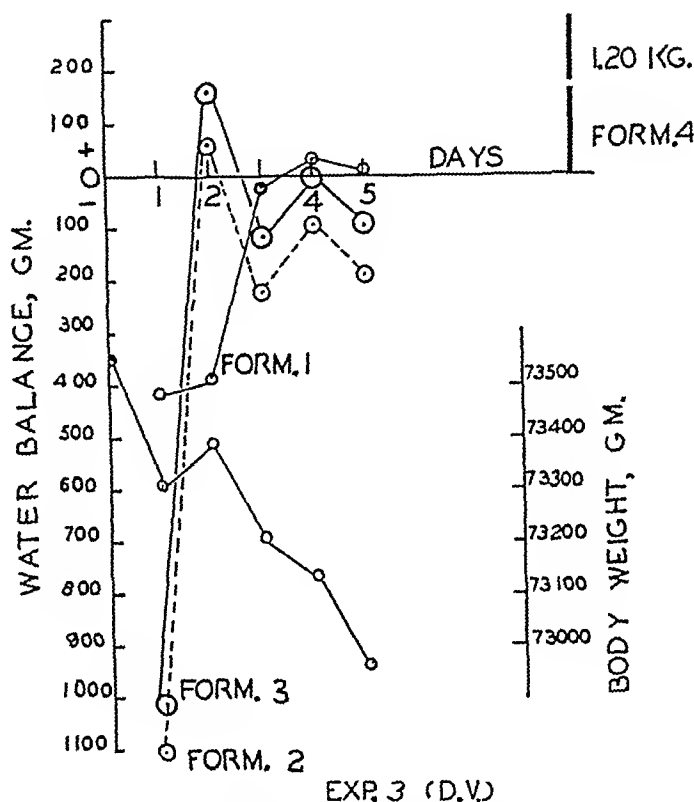


CHART 3.—Showing water balances in Experiment III. Subject D.V., at term.

The diet used in these experiments is believed to have been adequate. A period of adjustment to a new type of diet may, however, be required before a significant response may be expected. Attention is drawn to this point by Sherman:¹⁷ "That when the body is accustomed to a certain rate of protein metabolism, it requires an appreciable length of time to adjust itself to a materially higher or lower rate. Hence the rate of protein metabolism on any given day will depend in part upon the rate of metabolism to which the body has been accustomed and in part upon the protein intake for the day." If this is true for proteins, could thought be given to the idea that the conclusion may also apply to bases and to water? Perhaps the 5- to 11-day observation periods were too brief to permit the establishment of a definite response. Within that time no consistent trend of body weight was perceptible in our subjects.

vehicle, with all its potentialities as a lethal weapon, the situation takes on quite a different aspect, and little as we may be concerned with the final repository of his soul we have a genuine concern for his activities at the wheel. He presents a menace on the highway in the face of which no amount of precaution, superior equipment, or skill on the part of sober users of the roads may prevail, with the result that when he comes to grief the innocent must suffer with the guilty. Nor is he dangerous only when driving; as a pedestrian he also presents a serious problem by his presence on the road, not so much for his own safety, which one might be inclined not to value too highly, but because motorists in seeking to avoid striking him may precipitate themselves into another vehicle.

For these reasons, it is essential that the attitude of society, and its agency of enforcement, the law, be reformed regarding the offense variously entitled drunkenness, intoxication, and being under the influence of intoxicating liquor. However one may feel about society's responsibility for an individual's moral conduct, there can be no question about the necessity for safeguarding the lives and property of those with whom he comes in contact, even though it may entail certain restrictions of his activity. There thus arises the concept that a degree of alcoholic intoxication which need not cause an offense against society when the inebriate is in his own home may present a definite hazard to the public weal when he is on the public highway, either as the driver of a motor vehicle or as a pedestrian. The removal of such an individual from a position in which he endangers himself and others cannot be considered an infringement of personal liberty, but must be regarded as a deprivation for cause of certain special privileges.

We have been engaged in an experimental study of the relation of blood alcohol concentration to driving abilities, in an endeavor to work out some practicable yet just method for apprehending and convicting those individuals who present a hazard on the road because of indulgence in alcohol, and even more important to provide unbiased factual data for use in educating the driving public to a realization of the dangers of drinking and driving. In a previous study we⁵ showed that the effect of a given concentration of blood alcohol on performance of tests related to driving skill varied greatly from one individual to another, and that while there was a very definite tendency for those individuals with higher blood alcohol concentrations to show the greatest impairment of driving skill, this was by no means universally true. Since driving skill depends not on a few but rather on many component abilities, we felt it desirable to extend the studies by a consideration of the various factors involved in vision.

To this end a series of 50 drivers, 35 men and 15 women, were secured as volunteers from the general public and given a battery of 7 tests before and after taking alcohol. The dose of alcohol was

Although quantitative accuracy is not claimed, since various components of these formulas are based on assumptions, it is nevertheless felt that a study by these formulas promotes an understanding of the interrelated physiologic principles underlying water metabolism.

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THE EFFECT OF ALCOHOL ON VISION.

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A LARGE proportion of the research in alcohol during the past decade or so has been inspired in some degree by the increasing importance of the diagnosis of inebriation. Before the advent of popular use of the automobile, the hazards of drunkenness were largely confined to the inebriate and possibly his immediate family and associates. So long as he confined his activities to falling in stupor in the gutter, or throwing his boots at his wife's head when he returned home, he did not present an important threat to the public safety, and what efforts were made to curb his course were most often directed to saving his soul.

Now, however, when there is a fair probability that at some time during his debauch he will find himself in control of a motor

DEPTH PERCEPTION. Depth perception was tested by the Keystone Telebinocular using the depth perception slide. This is a 10-line chart, each line representing 10%. A drop of 10% was con-

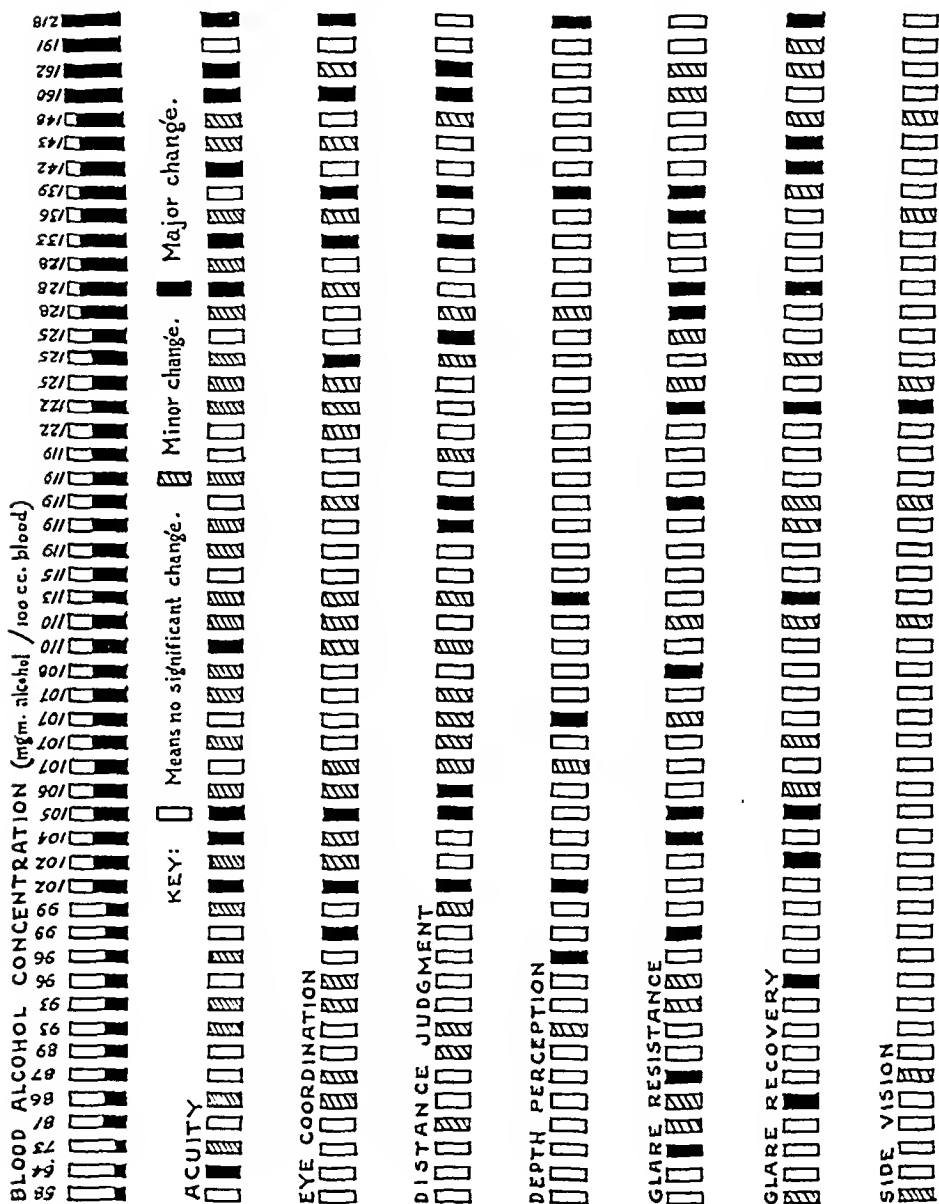


Fig. 1—Showing blood alcohol concentration and its effect on several visual abilities in fifty drivers after drinking. Each individual's record is shown vertically.

sidered significant, and a drop of 20% a major change. Eighteen per cent of the subjects showed at least a 10% change, and 12% showed 20% or more decrease.

less strictly controlled than in the previous study, a basic dose of an ounce of whisky for each 30 pounds of body weight being required of all subjects, with the option of more if desired, the whole dose being consumed in from 15 to 30 minutes. This variation in dose, coupled with the fact that some of the subjects were not in a fasting state, accounted for the considerable range of blood alcohol concentrations apparent in Figure 1. We were thus able to study the effect of a wide variety of blood alcohol concentrations, at the expense of not having a large number of cases at any one concentration.

A choice of a good commercial brand of Scotch or Bourbon whisky of approximately 90 proof, diluted as desired with carbonated water and cooled with ice, was provided, and the drinking was done in a social atmosphere. Thus the drinking situation was a fairly normal one, with a minimum of tension due to the test situation.

The tests were such as to require the minimum of instruction and to show the least effect of practice, as will be evident from their description. About 10 minutes were required for their administration. The subject was given the tests just prior to drinking, and again 45 minutes after drinking was completed, so that absorption in most cases was practically complete and a maximum blood alcohol concentration achieved at the time of the second testing, at the end of which period a sample of venous blood from an arm vein was taken for alcohol analysis, using the method of Newman.⁴

The results on all the tests, and the blood alcohol concentrations achieved by each subject, are shown graphically in Figure 1. We will now describe each test, the criteria of scoring, and the results obtained, and then proceed to a discussion of the results. It should be noted that in reporting the results, major changes in performance are indicated by a separate figure, while the figure for significant changes includes these major changes as well as important minor changes.

VISUAL ACUITY. Visual acuity was tested in each eye separately by the Keystone Telebinocular instrument, using the slides for acuity measurement. The 100% mark on this instrument is equivalent to 20/20 on the Snellen chart. A drop in acuity of 5% was considered significant, and a drop of 20% a major drop. In this connection, it should be noted that a drop from 100% to 80% is equal to a drop from 20/20 to 20/45 on the Snellen chart. Seventy per cent of the drivers showed a significant decline in visual acuity, while 22% showed a major drop of 20% or more, the major changes increasing with the alcohol concentration. It was more than twice as likely that one eye would be affected than both, the left eye being affected twice as often as the right. As alcohol concentration increased, the tendency was for both eyes to be affected. Most significant was the fact that the deficient vision was rarely recognized by the subject.

siderable intensity flooding the subject's field of vision when turned on. With this light off, the subject identifies the position of the arrow. It is then withdrawn from the field of vision and the headlight turned on, its intensity being gradually increased over a period of 20 seconds to a constant intensity, held at this level for an additional 20 seconds, and then extinguished abruptly. The arrow is returned to its original position in the box, pointing in a different direction, and the time required for the subject to correctly report its direction recorded with a stop-watch. A change of 5 seconds or more in recovery time was considered significant, and a change of 15 seconds a major change. Forty-two per cent of the drivers showed significant adverse changes, and 20% major adverse changes. It should be mentioned in this connection that in a number of cases, particularly those with an initially good performance, an improvement in recovery from glare was noted. This is in accord with experimental work done elsewhere,^{1,2,6} which demonstrated that the improvement was due to liberation of vitamin A from the liver by the alcohol. Of the subjects tested, 30% showed a significant speed-up in recovery time, and 12% showed a major improvement.

Discussion. The only similar experimental study, with the exception of the work on dark adaptation already noted, was reported by Colson³ in 1940. He tested 21 subjects for visual acuity, near vision, color vision, fields, muscle balance, and dark adaptation after administration of from 8 to 20 ounces of whisky. No determination of blood alcohol concentration was made. He found no change in acuity, near vision, or fields. If dark adaptation was initially normal, no change occurred; but if poor, it decreased. There was a shift in muscle balance, original exophoria becoming esophoria and *vice versa*. These negative findings are not entirely in accord with our work, while the failure to find improvement in dark adaptation in some cases, as found both by ourselves and other workers, is hard to explain.

From the data which we have presented, it can readily be seen that alcohol is capable of producing changes in all the components of vision tested by us. That all components are not affected in the same individual is amply demonstrated by Figure 1, which shows the distribution of major and significant changes in the various subjects. Also, although there is evident an obvious tendency for individuals with higher blood alcohol concentrations to show more changes, particularly major changes, this is far from true in every case. To elucidate this point further, the subjects were divided roughly into 3 groups on the basis of blood alcohol concentration. The first group, which we will call "mild concentration," consisted of 13 individuals with blood alcohol concentrations under 101 mg. per 100 cc.; the second group, "moderate concentration," consisted of 24 subjects with blood alcohol values from 101 to 125 mg. per

DISTANCE JUDGMENT. Distance judgment was tested with the Army Rod Test at a distance of 20 feet. A series of 4 trials was given, and the worst of these, exclusive of the first trial, was taken as the standard of performance. A decrease in ability after drinking of over $\frac{1}{2}$ inch was considered a significant, and a decrease of over 1 inch a major change. On this test 48% showed significant and 18% major decreases.

LATERAL FIELDS OF VISION. The subject's ability to see to the side while looking straight ahead was tested by means of the Brombach Perimeter. A white target, $\frac{3}{4}$ inch in diameter, was used, and the measurement taken at the point of awareness of the target when moved slowly toward the center, so that mass fields rather than form or motion fields were secured. A decrease of 3 degrees or more from the non-alcoholic level was considered a significant change, while a 10 degree decrease was a major change. Sixteen per cent of the drivers showed significant decreases, while but 1 showed a major change.

EYE COÖRDINATION. The balance and fusion of the eyes was tested by using the Keystone Telebinocular with slides for measuring fusion, vertical balance, and lateral balance. In all tests with this instrument the driving range, at 20 feet or more, was used. In this test, experience and judgment had to be employed in rating the deficiencies. If a significant change took place in 2 or more of the components, or if fusion could not be accomplished, a major change was recorded. After alcohol, 54% of the subjects showed significant changes, 18% major changes.

GLARE RESISTANCE. The ability to resist glaring headlights and to see objects in the darkness beyond them was tested by means of apparatus developed by the Division of Drivers Licenses and the College of Engineering, University of California at Berkeley. In brief, the subject, on looking into a darkened box, gazes down a roadway. He sees the headlights of an approaching car directed straight at him, remaining fixed in position and intensity. In the box, directly below the subject's eyes, is a controllable beam of light representing his headlights. This beam can be varied in 20 steps of intensity, and the intensity at which he can just discern a white shape beside the approaching headlights is considered the index of glare resistance. A drop of 2 steps or more was considered a significant change, of 3 steps a major change.

GLARE RECOVERY. The speed of recovery from glaring lights was measured by means of a glare recovery test built by Dr. C. W. Brown, Dept. of Psychology, Univ. of California, at Berkeley. In this apparatus the subject gazes into a darkened box and, by the illumination of a small constant pilot light, is able to tell the direction in which an arrow controlled by the examiner is pointing. Back of the arrow is set the lens, reflector, and bulb of an automobile headlight so arranged as to produce a diffused light of con-

from glare increased from 51 to 138 seconds, and he became unable to fuse on eye coordination.

Subject B showed a blood alcohol concentration of 191 mg. per 100 cc., far above the 150 mg. per 100 cc. standard, and almost twice that of Subject A. Yet the only change he showed in the tests was an increase in time of recovery from glare from his original excellent performance of 24 seconds to a final performance of 34 seconds, still within the normal range. There was no evidence from any of the tests that he was unable to drive a car in the manner of an ordinarily prudent and cautious person in full possession of his faculties, yet he would have stood convicted of drunken driving under the 150 mg. per 100 cc. standard proposed by the National Safety Council, no other evidence than his blood alcohol concentration being necessary for this conviction. On the other hand, Subject A, with marked impairment in the majority of the tests would, because of his much lower blood alcohol concentration, have to be proven guilty on the basis of other evidence, and would have the privilege, denied to Subject B, of defending himself against the charge. It seems to us that these 2 cases, selected from a very small material, are amply indicative of the injustice of setting up, in the light of our present limited knowledge, any minimum standard of blood alcohol concentration, the exceeding of which would constitute *prima facie* evidence of intoxication, or of using blood alcohol concentration as the sole criterion of intoxication. Rather let us retain the undoubted benefits of the chemical diagnosis of intoxication in revealing the minimum amount of alcohol a suspect has consumed and indicating, in conjunction with other evidence, the probability of intoxication having existed, than destroy the value and credibility of the whole procedure by ascribing to it an infallibility which it does not possess.

Summary and Conclusions. Fifty drivers were each given 7 tests concerned with vision before and after imbibition of alcohol in a dose of at least an ounce of whisky for each 30 pounds of body weight. The resultant concentrations of alcohol in the blood varied from 58 to 218 mg. per 100 cc.

In every case with a concentration over 115 mg. per 100 cc. a significant change in at least one of the tests was found. The greatest number of changes occurred in visual acuity, the smallest in field of vision.

Although there was a definite tendency for those with the higher blood alcohol concentrations to show more changes, this was far from true in every case.

These findings support the contention that there exists a considerable individual variation in tolerance to a given concentration of alcohol in the blood, and indicate the importance of recognizing the limitations of blood alcohol concentration as the sole criterion of intoxication.

100 cc.; and the third, "medium concentration," consisted of 13 subjects with blood alcohol values over 125 mg. per 100 cc. The percentage of significant and major changes in each of these groups is tabulated in Table 1. The rather poor correlation between blood alcohol concentration and changes in visual function is quite apparent, especially in regard to significant rather than major changes. It would indeed be impossible to select any single level of blood alcohol concentration as a criterion of dangerous intoxication from these data. Certainly a figure of 150 mg. per 100 cc., proposed as *prima facie* evidence of drunkenness by the National Safety Council, would be definitely too high for some of the subjects, and equally definitely too low for others. To illustrate this point, which is of great importance in view of pending legislation in several States, let us summarize the findings in two subjects with widely different blood alcohol concentrations.

TABLE 1.—RELATIVE EFFECT OF MILD, MODERATE, AND MEDIUM BLOOD ALCOHOL CONCENTRATIONS ON VARIOUS COMPONENTS OF VISION.

(The percentage recorded as significant decrease includes also those subjects showing major decrease.)

Test.	Significant decrease, %.	Major decrease, %.
<i>Acuity:</i> Mild concentration	54	8
Moderate concentration	71	17
Medium concentration	85	46
<i>Depth Perception:</i> Mild	15	8
Moderate	17	12
Medium	23	15
<i>Distance Judgment:</i> Mild	31	0
Moderate	58	21
Medium	46	31
<i>Eye Coordination:</i> Mild	38	8
Moderate	59	12
Medium	62	31
<i>Glare Resistance:</i> Mild	54	23
Moderate	37	21
Medium	46	31
<i>Glare Recovery:</i> Mild	23	15
Moderate	42	17
Medium	62	31
<i>Side Vision:</i> Mild	15	0
Moderate	17	8
Medium	15	0

Subject A had at the time of the test a blood alcohol concentration of only 105 mg. per 100 cc., well below the limit of 150 mg. per 100 cc. proposed as definite evidence of intoxication. Yet he showed a major drop after alcohol in 5 of the 7 tests. Only in depth perception, which was poor to begin with, and in side vision did he maintain his performance. His left eye dropped 50% in acuity (which means a drop from a Snellen rating of 20/20 to 20/100), error in distance judgment increased from $1\frac{3}{4}$ to $4\frac{1}{8}$ inches, glare resistance dropped from 6.5 to 3.5 units (or 6 steps), recovery time

weight, each patient received 100 gm. of glucose dissolved in water. One hour later a second blood sugar and 2 hours later, a third blood sugar were taken. In a few cases blood sugars were obtained at more frequent intervals after the administration of glucose.

Case Reports. CASE 1.—J. M., male, aged 55, weight 104 pounds, which is about 20 pounds less than his normal. Glycosuria was discovered in 1936 and a diet of CH 120, P 90, F 135 was given. A glucose tolerance curve done 5 days after the beginning of the diet showed a definite impairment of his tolerance (6/24/36) (Chart 1). Nevertheless, his urine became sugar-free. The carbohydrate content of the diet was raised gradually with a simultaneous reduction of the protein and fat until August, 1939, when he was receiving CH 250, P 75, F 70. A glucose tolerance curve at this time showed a definite improvement (8/24/39). Further increasing the carbohydrate content of the diet to 300 gm. resulted in a loss of tolerance (7/3/40). Later, decreasing the carbohydrate intake to 200 gm. produced only a slight improvement (9/25/40). The glucose tolerance curve indicated that the tolerance of the patient for carbohydrate was not as high on this diet as on the CH 250 diet.

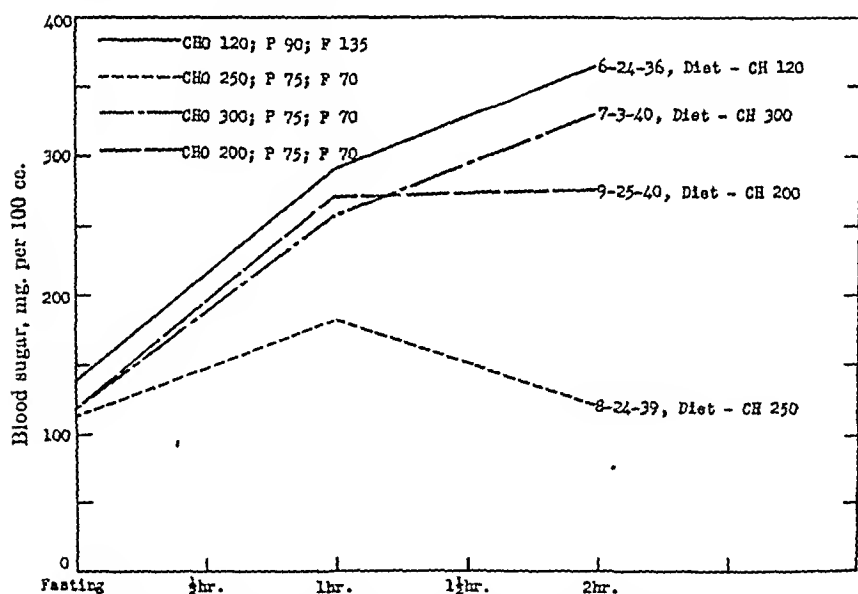


CHART 1.—Case 1. Mild diabetes. Male, age 55, underweight. Improved glucose tolerance on diet of CH 250, P 75, F 70. Loss of tolerance as diet is raised to CH 300 or lowered to CH 200. Conclusion: glucose tolerance improved on diet of CH 250. Raising or lowering CH of diet results in a loss of tolerance.

This man's optimal carbohydrate intake evidently is 250 gm. When maintained on this diet there is a minimal impairment of his glucose tolerance. A diet containing more or less carbohydrate than this results in a loss of glucose tolerance (Chart 1).

CASE 2.—E. G., 42-year-old diabetic female, weight 154 pounds, which was 22 pounds in excess of the normal for her height and age. A diet of CH 100, Cal. 1200 was prescribed. After a loss of 18 pounds, a glucose tolerance curve suggested a mild impairment of carbohydrate tolerance

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THE DIABETIC STATE AS INFLUENCED BY DIET.

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THE optimal diet for the treatment of diabetes has not been established despite the fact that the kind of food eaten plays so vital a part in the management of this disease. The mode of feeding the diabetic has run the gamut from the extremely low-carbohydrate, high-fat regimen of the pre-insulin era, to the very high-carbohydrate, low-fat diets advocated more recently.

The influence of the composition of the diet upon the capacity of the diabetic to utilize sugar has been debated for a long time. A generation ago the dictum of Naunyn⁵ was generally accepted. He maintained that the surest way to increase the carbohydrate tolerance in diabetes was to restrict carbohydrates to the limits of the diabetic's power to utilize glucose. The efficiency of this scheme of dietary treatment has recently been demonstrated in experimental animals by Haist, Campbell and Best.⁴

In normal persons a low-carbohydrate diet diminishes glucose tolerance, while a persistent intake of large amounts of starch will increase it. Conn² has recently reviewed the literature on this subject and verified it by clinical tests. These well-established findings in non-diabetics have been regarded as confirmatory evidence that a high-carbohydrate diet has a beneficial effect in diabetes. Indeed, various clinicians have found that a high-carbohydrate diet was a potent factor in rehabilitating the depressed carbohydrate tolerance in diabetes (Aldersberg and Porges;¹ San-sum, Blatherwick and Bowden;⁷ Geyelin;³ Rabinowitch⁶).

Because of these contentions it was of interest to study the effects of high and low-carbohydrate diets in a series of mild diabetics. None of these patients received insulin while under observation. Glucose tolerance tests were used to determine the variations in carbohydrate tolerance. The tests were standardized in the following manner: a fasting blood sugar was taken. Regardless of

tolerance (Chart 4). His diet was raised to CH 250 and a week later a glucose tolerance test showed a definite loss of tolerance.

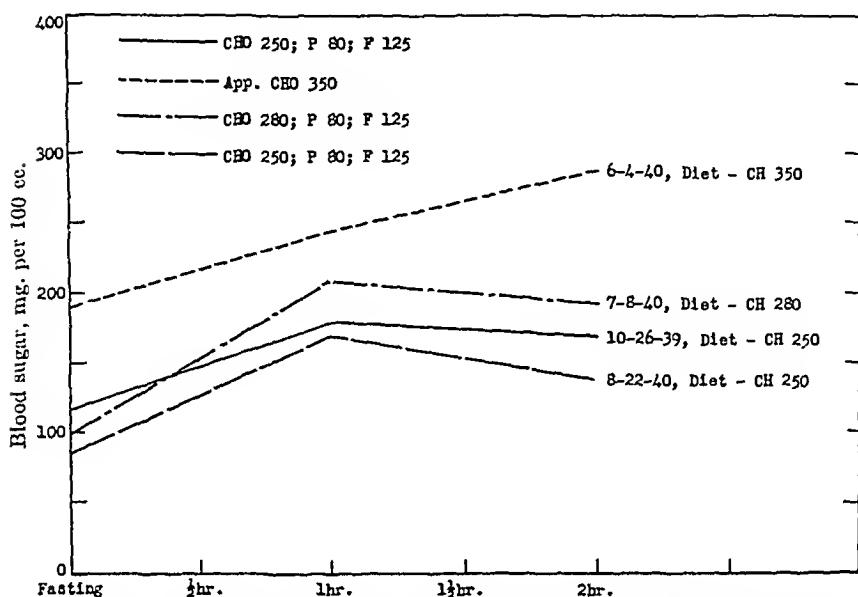


CHART 3.—Case 3. Male, age 52, normal weight. Mild impairment of glucose tolerance on CH 250, P 80, F 125. Raising carbohydrate intake above this level diminishes tolerance. Conclusion: very high-carbohydrate diet impairs carbohydrate tolerance.

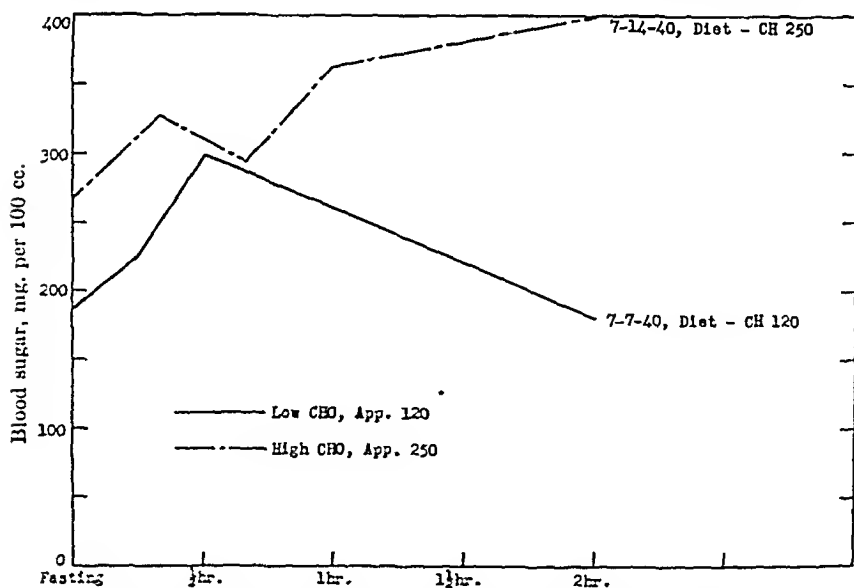


CHART 4.—Case 4. Male, age 47. Impaired glucose tolerance on CH 120. Definite loss of tolerance on CH 250. Conclusions: high-carbohydrate diet results in loss of glucose tolerance.

(5/24/38) (Chart 2). A higher carbohydrate diet was ordered but because the patient was "afraid to eat," the original diet was continued with no further loss of weight. A glucose tolerance curve on June 7, 1939, was similar to the one done a year earlier. Because of her concern over her weight loss, the diet was raised to CH 300. After 6 months of this diet there was no change in weight but a glucose tolerance curve (1/17/40) indicated a loss of tolerance (Chart 2). The carbohydrate content of the diet was then restricted to 150 gm. and 6 months later (8/20/40) the glucose tolerance curve was definitely normal. It showed a distinct improvement as compared with the curves on the previous diets.

This patient's optimal carbohydrate intake is apparently 150 gm. Raising the carbohydrate of the diet above this level to 300 gm., or lowering it to 100 gm. result in a loss of tolerance (Chart 2).

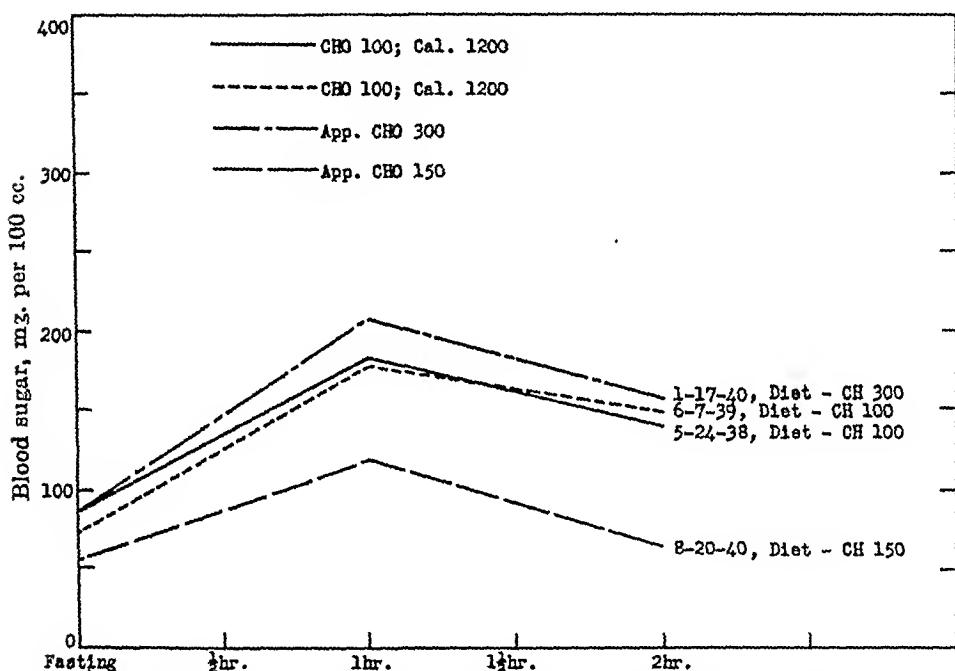


CHART 2.—Case 2. Mild diabetes, female, age 42, weight 154 pounds; 20 pounds overweight for height and age. After a loss of 18 pounds on CH 100, Cal. 1200, glucose tolerance curve indicates a mild impairment of CH tolerance. Further slight loss of tolerance when diet is raised to CH 300. Marked improvement on CH 150. Conclusion: glucose tolerance diminishes when diet is raised above or below the level of CH 150.

CASE 3.—S. G., male, aged 52, weight 159 pounds, which is normal. A glucose tolerance test while on a diet of CH 250, P 80, F 125 indicated a mild impairment of tolerance (10/26/39) (Chart 3). Raising the diet to CH 350 resulted in a definite loss of tolerance (6/4/40). Some improvement was noted on a diet of CH 280 (7/8/40) but definite improvement did not occur until the diet was reduced to CH 250 (8/22/40).

This patient's most advantageous carbohydrate allowance is evidently 250 gm. and a carbohydrate intake in excess of this amount results in a loss of tolerance (Chart 3).

CASE 4.—J. F., male, aged 47, an established diabetic, had been on a diet of approximately CH 120 for several years. On July 7, 1940, a glucose tolerance curve showed that there was a moderate impairment in his

and age is 133 pounds. When she was at her maximum weight a glucose tolerance curve indicated a definite impairment. After a loss of 51 pounds, there was a marked improvement in her glucose tolerance (Chart 5). An anti-obesity diet, low in carbohydrate and fat but high in protein, was followed throughout the period of observation.

CASE 6.—R. G., aged 24, weight 140 pounds which was 25 pounds in excess of the normal. A glucose tolerance test on May 16, 1940, indicated an impairment of her carbohydrate metabolism (Chart 6). During the next 6 months there was a loss of 22 pounds on a diet of CH 100, Cal. 1000. A glucose tolerance test on February 12, 1941, was normal. The low carbohydrate diet continued over a period of 9 months evidently resulted in an improvement in this patient's tolerance for carbohydrate (Chart 6).

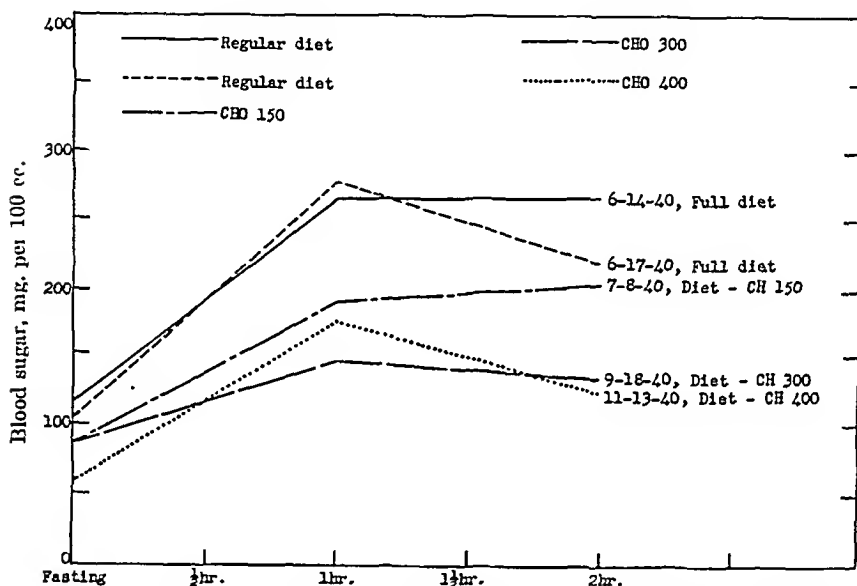


CHART 7.—Case 7. Female, age 18, mild diabetes, weight normal. Tolerance improved as diet is raised from CH 150 to CH 300 and later to CH 400. Conclusion: increase in glucose tolerance on a high-carbohydrate diet.

CASE 7.—B. M., female, aged 18 years, weight 121 pounds, which was normal. While on a full diet, including sugar, glucose tolerance curves on two occasions (6/14/40 and 6/17/40) showed a definite impairment in tolerance for carbohydrate (Chart 7). The diet was restricted to CH 150. Three weeks later (7/8/40), a glucose tolerance curve indicated a distinct improvement in carbohydrate tolerance. The diet was increased to CH 300. Two months later (9/18/40) her glucose tolerance was definitely normal. Again, the diet was increased to CH 400 and again 2 months later (11/13/40) the glucose tolerance curve was normal. The tolerance of this patient for carbohydrate increased when the diet was raised to CH 300 and showed very little change on a CH 400 diet. On a diet lower than CH 300, however, there was a mild impairment of carbohydrate tolerance (Chart 7).

Conclusions. The carbohydrate tolerance in many diabetics may be increased by diet. The type of diet, whether high- or low-carbohydrate, is not the determining factor but the important principle

The tolerance of this patient for carbohydrate is evidently about 120 gm. and raising the carbohydrate intake above this results in a loss of tolerance.

CASE 5.—(Courtesy of Dr. Abraham Levy.) G. A., female, aged 34, height 62 inches, weight 215 pounds. The normal weight for her height

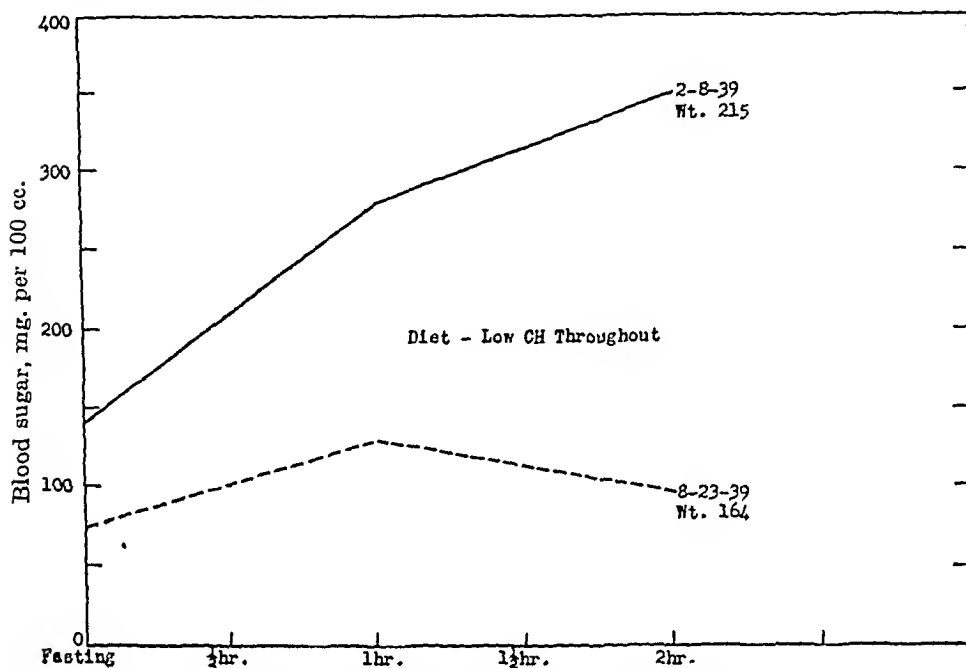


CHART 5.—Case 5. Loss of 51 pounds results in an improvement in glucose tolerance, while on a low-carbohydrate diet for a prolonged period.

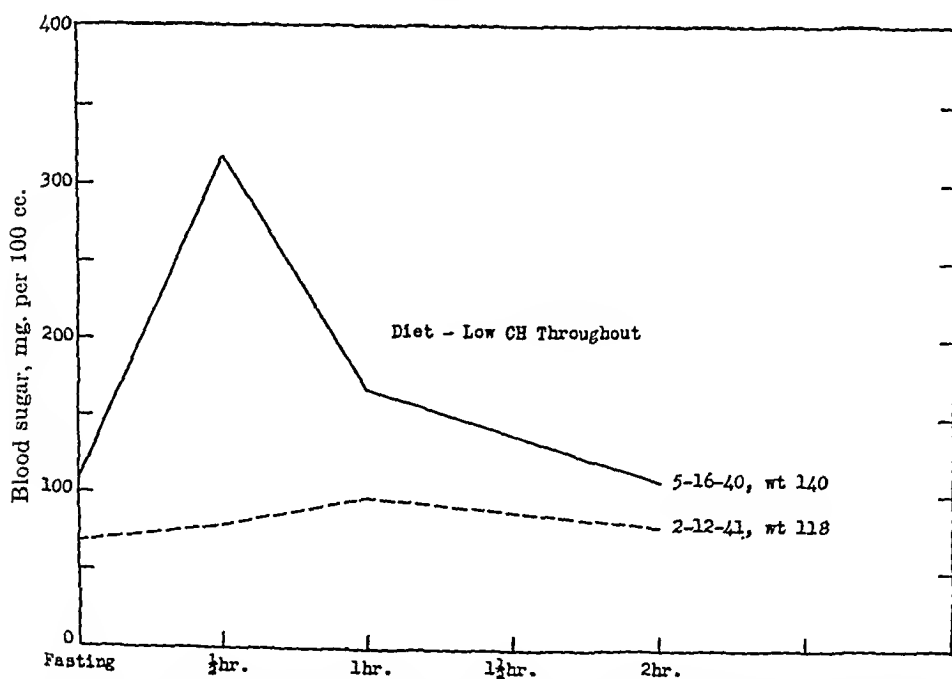


CHART 6.—Case 6. Loss of 22 pounds brought about by means of low-carbohydrate diet results in an improvement in glucose tolerance.

the vessels of the neck. Because this form of angina pectoris has received only limited attention in the literature, it is believed that a report of 6 additional cases should be of interest.

Case Reports. CASE 1.—*Rheumatic heart disease, enlargement of the heart, aortic insufficiency and probable stenosis, mitral insufficiency, angina pectoris.* A white boy of 18 came to the Clinic on December 28, 1939, because of severe paroxysmal pain in the chest. He had had rheumatic fever at the age of 8 years and again 2 years later. One year before his admission, he began to experience attacks of severe, clutching pain in the precordial and upper substernal areas. The pain radiated to the left side of the neck, left shoulder and down the inner aspect of the left arm to the fingers. Occasionally there was radiation down the right arm as well. The attacks were accompanied by dyspnea, orthopnea, a sense of suffocation, severe palpitation and throbbing of the vessels of the neck. Occasionally they were precipitated by exertion, excitement or exposure to cold, and at times they developed with little or no provocation after a large meal. The most severe and most frequent seizures, however, occurred at night and wakened him from sleep. There had been from one to three attacks per week, and the usual duration of the pain was from 5 to 30 minutes. The seizures which were brought on by exertion were relieved by rest, but for those which occurred at night the only helpful measure consisted of sitting on the edge of the bed or standing. Occasionally some added benefit seemed to result from swinging the left arm in circles at the shoulder.

Physical examination revealed a well-developed, well-nourished individual. The temperature was normal, the pulse rate 84 per minute and the blood pressure 150 mm. systolic and 20 mm. diastolic. There was forcible pulsation of the vessels of the neck, and capillary pulsation, Duroziez's sign and a waterhammer pulse were present. The heart was greatly enlarged. A systolic thrill was felt over the aortic area, and the aortic second sound could not be heard. Loud systolic and diastolic murmurs were present over the aortic area, and the diastolic murmur was transmitted downward along the left border of the sternum. A moderate systolic and a transmitted diastolic murmur were present over the apex. There were no signs of congestive heart failure.

Roentgenologic examination of the chest showed the left ventricle to be greatly enlarged. There was no prominence of the pulmonary artery and conus, and the right anterior oblique plate revealed no enlargement of the left auricle. An electrocardiogram showed nothing of significance except for moderate left axis deviation. Urinalyses, blood counts, and the erythrocyte sedimentation test all gave results within the limits of normal, and the Wassermann reaction of the blood was negative.

Cervico-dorsal laminectomy with section of the posterior roots of the first five thoracic nerves on both sides was done on January 3, 1940. The post-operative course was uneventful although on two occasions before leaving the hospital the patient was awakened at night with mild pain in both sides of the neck.

Eleven months after the operation, the patient reported that he was still experiencing attacks of pain once or twice a week or less often. The pain was confined to the sides of the neck from the clavicles to the lobes of the ears and was more severe on the left side than on the right. Occasionally there was radiation of the pain down the inner aspect of the left arm to the wrist. The attacks could be brought on by exertion or excitement but usually occurred at night. They were still accompanied by rapid, forceful heart action, throbbing of the vessels of the neck, sweating of the face and neck, dyspnea and weakness. Nitroglycerin, $\frac{1}{16}$ gr., invariably gave prompt relief.

is the feeding of the patient with the maximum amount of carbohydrate which can be utilized. When this is carried out the carbohydrate tolerance is likely to increase whether the diet required is high or low in carbohydrate content.

If the quantity of carbohydrate taken by a diabetic exceeds his tolerance the severity of the diabetes will increase. This is in contrast to the normal person who invariably loses glucose tolerance on a low-carbohydrate diet, and gains with a high-carbohydrate diet.

Consequently, there is no uniform optimal carbohydrate content for diabetic diets. Each case must be evaluated according to the requirements of the individual.

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ANGINA PECTORIS IN YOUNG INDIVIDUALS WITH AORTIC INSUFFICIENCY.

A REPORT OF 6 CASES

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THERE is a form of angina pectoris that differs in important respects from the form due to coronary artery disease. The condition occurs in young individuals, and the significant anatomic lesion associated with it consists of pronounced aortic insufficiency of rheumatic origin. The pain is similar in location, quality and radiation to that of the common form of angina pectoris, and the attacks may be induced by effort or excitement. The most important distinguishing characteristic of the syndrome, however, consists of the occurrence of nocturnal seizures, and it is these attacks that usually constitute the principal complaint of the patient. The nocturnal attacks are extremely severe, usually last 10 to 20 minutes, and frequently recur several times during a night. Nitroglycerin usually gives prompt relief, but patients who have had no treatment often report that the only spontaneously beneficial measure consists of getting up and walking about. The attacks are further distinguished by the common occurrence of prominent vasomotor changes such as flushing of the face, sweating, palpitation and throbbing of

increased gradually in frequency, and at the time of the patient's admission they occurred at least once a week and often several times a night. Tachycardia, palpitation, dyspnea, profuse perspiration, and a generalized feeling of warmth accompanied the pain but no changes in color had been noted. Occasionally there was radiation of the pain to the left shoulder. No medication had been employed, and the only measure which had been found to give relief consisted of standing up and moving about. The duration of the attacks varied from a few seconds to 15 minutes.

On *physical examination*, the temperature was normal, the pulse rate 110 per minute, and the blood pressure 132 mm. systolic and 50 mm. diastolic. The area of relative cardiac dullness extended 13 cm. to the left of the mid-sternal line in the sixth interspace. The heart rhythm was regular. Over the aortic area a short systolic and a long low-pitched diastolic murmur were heard, the latter being transmitted downward along the left border of the sternum. Systolic and diastolic murmurs also were present at the apex. There were no signs of congestive heart failure. Capillary pulsation was present, and the pulse wave was of the waterhammer type.

Roentgenograms of the chest showed enlargement of the outflow tract of the left ventricle. A right anterior oblique plate revealed no enlargement of the left auricle. The electrocardiogram showed slurring of the *QRS* complexes with notching in Leads I and III, diphasic T_2 , inverted T_3 , and a normal electrical axis. The blood count and urinalyses gave normal findings, and the Wassermann reaction of the blood was negative.

Paravertebral alcohol injection of the upper four dorsal sympathetic ganglia on the left side was performed on September 14, 1938. One month later the patient reported that the attacks had not diminished in frequency but had lessened some in severity. Three months later, however, the seizures had almost ceased to recur and those which were experienced were mild and of short duration.

CASE 4.—*Rheumatic heart disease, enlargement of the heart, aortic insufficiency, mitral stenosis and insufficiency, angina pectoris.* A white salesman of 24 years came to the Clinic on December 27, 1935, because of attacks of pressure-like epigastric and lower substernal pain during the preceding 2 years. The symptoms often appeared after a large meal and at other times were induced by excitement or by exertion in cold weather. Most of the attacks, however, occurred at night and wakened him from sleep. Getting out of bed and standing up would give relief in 15 or 20 minutes. The pain was accompanied by palpitation and dyspnea and often by dull aching pain over the inner aspect of the left arm down to the wrist. The patient had had rheumatic fever at the age of 16 years.

On *physical examination*, the left border of the heart was 14 cm. from the mid-sternum in the sixth interspace. The heart rhythm was regular and the rate 80 per minute. Systolic and diastolic murmurs were present over the aortic area, and the diastolic murmur was transmitted downward along the left border of the sternum. Over the apex a harsh systolic and a loud diastolic murmur with presystolic accentuation were heard. The radial pulse wave was of the Corrigan type, and Duroziez's sign and capillary pulsation were present. The arterial blood pressure was 190 mm. systolic and 40 mm. diastolic. There were no signs of congestive heart failure. The blood count and urinalysis gave normal results, and the Wassermann reaction of the blood was negative.

Because of unpleasant side actions, the use of nitroglycerin was refused. The attacks increased steadily in frequency and severity and continued to occur more often at night than at other times. For several months before his death he was forced to stand up a large part of each night. He died in his sleep on September 2, 1939, after having worked as usual on the preceding day.

CASE 2.—*Rheumatic heart disease, enlargement of the heart, aortic insufficiency and probable stenosis, mitral stenosis and insufficiency, angina pectoris.* A white man of 21 first came to the Clinic on June 15, 1936, at which time a diagnosis of rheumatic heart disease was made. He returned 2 years later complaining of frequent attacks of severe, gripping, non-radiating pain in the mid-substernal region. The pain was accompanied by palpitation, flushing of the face and sweating, but there was no dyspnea. The attacks almost always occurred at night, awakening him from sleep, and at times the mere act of lying down precipitated a seizure. Occasionally the sudden beginning of activity after a period of rest would induce the pain, but except for this there had been no relationship between the attacks and exertion. Amyl nitrite or nitroglycerin gave prompt relief from the pain, and it had been necessary to repeat the use of these drugs as many as 20 times during a single night.

Physical examination revealed a tall, thin individual. The temperature was normal, the pulse rate 84 per minute and the blood pressure 188 mm. systolic and 30 mm. diastolic. There was forcible pulsation of the vessels of the neck. Duroziez's sign and capillary pulsation were present, and the pulse wave was of the collapsing type. The heart was enlarged, and a coarse systolic thrill could be felt over the base and in the vessels of the neck. Loud systolic and diastolic murmurs were present over the aortic area, while at the apex a moderate systolic and a faint diastolic murmur with a definite terminal crescendo were heard. There were no signs of congestive heart failure.

Roentgenologic examination of the chest showed enlargement of the left ventricle and straightening of the upper left border of the heart. The right anterior oblique plate showed enlargement of the left auricle. An electrocardiogram revealed sinus rhythm, notched *P* waves in all leads, deep inversion of *T*₁ and *T*₂, increased amplitude of *QRS*₁, slurring of *QRS*₂, notching of *QRS*₃, and left axis deviation. Urinalyses, blood counts and the erythrocyte sedimentation test all gave results within the limits of normal. The Wassermann reaction of the blood was negative.

Excision of the inferior cervical and upper four dorsal sympathetic ganglia on the left was performed on August 5, 1938. Five months later the patient reported that the attacks had not diminished in frequency, although the pain was possibly somewhat less severe. The seizures now occurred only at night; there had been no attacks as a result of exertion. For some reason amyl nitrite and nitroglycerin had not been used, and the patient was taking 5 or 6 gr. of codeine sulphate plus large amounts of whisky each night. He reported, however, that the most helpful measure he had found consisted of stretching his arms above his head and supporting himself from a door frame. Except for a Horner's syndrome on the left side, the physical examination revealed no changes from the findings recorded previously.

Paravertebral alcohol injection of the inferior cervical and upper four dorsal sympathetic ganglia on the right was done on January 12, 1939. This procedure resulted in no improvement. Two years later the patient was using 100 nitroglycerin tablets every 8 to 15 nights.

CASE 3.—*Rheumatic heart disease, enlargement of the heart, aortic insufficiency, mitral insufficiency, angina pectoris.* A white, married woman of 30 came to the Clinic on September 12, 1938, because of severe, paroxysmal pain in the substernal region. She had had rheumatic fever at the age of 12 years, and 6 years later had experienced her first attack of pressure-like pain in the chest. At first the seizures occurred at infrequent intervals and there were periods of as long as 6 months without symptoms. The attacks always occurred at night and were never induced by exertion. Dreams seemed to be an important precipitating factor. The seizures had

anterior oblique plate revealed great enlargement of the left auricle. An electrocardiogram showed deep inversion of T_1 and T_2 , slight inversion of T_3 , and a normal electrical axis. The urinalysis and blood count gave normal findings. The Wassermann reaction of the blood was 4+.

On the afternoon of the patient's admission, he was seen in an attack. There was agonizing pain, the face was pale, and there was profuse, clammy perspiration. The neck vessels were throbbing forcibly, and the patient complained of palpitation and dyspnea. The pulse rate was 84 per minute, but the blood pressure had increased to 200 mm. systolic and 40 mm. diastolic. The symptoms were relieved promptly by nitroglycerin, $\frac{1}{320}$ gr.

Strictly limited activity was advised, and the patient was directed to take nitroglycerin before each meal and as necessary for the attacks. One month later he reported that the seizures were less frequent and less severe but that they still occurred several times each day and once or twice every night. Death occurred on September 14, 1938.

Discussion. Although isolated examples of the syndrome illustrated by these cases had been reported earlier, the clinical features of the condition were first delineated by Schwartz¹⁰ and White and Mudd.¹⁴ Additional cases were reported subsequently by Stolkind,¹² Levin,⁷ Korns,⁶ Lewis,⁸ Eakin,⁴ and Bland and White.³ Keefer and Resnik⁵ also mention having observed 4 patients who had rheumatic aortic insufficiency and angina pectoris. The syndrome, however, is uncommon, and the total number of cases reported is still well under 100.

Vaquez¹³ reviewed the earlier literature concerning the existence of two varieties of angina pectoris distinguished by the terms "angina pectoris of effort" and "angina pectoris of decubitus." He described the two forms in detail, and although he did not associate angina of decubitus with aortic insufficiency, he did recognize that this variety occurred in individuals in whom the left ventricle was greatly enlarged and there was little or no coronary artery disease. He pointed out that individuals who have angina pectoris of decubitus may also experience attacks of pain on effort and was of the opinion that this mixed form was due to the presence of coronary artery disease or aortic atheroma in addition to an enlarged heart. The cases described in the present report illustrate the clinical features of angina pectoris of decubitus and demonstrate the dependence of the syndrome upon the presence of free aortic insufficiency. It should be emphasized that in 4 of the 6 patients attacks of pain also were induced by exertion, and yet the age of the patients was such that there was no ground for assuming the presence of coronary artery sclerosis.

It is generally accepted that the pain of angina pectoris is due to relative anoxemia of the myocardium.⁵ In aortic insufficiency, coronary bloodflow is diminished because of the lowered diastolic blood pressure and the reduced mean aortic pressure.^{1,2,11} It is readily understandable, therefore, how in a young individual with aortic regurgitation, an increase in the demands upon the heart incident to physical exertion can result in a sufficient degree of myocardial

CASE 5.—*Rheumatic heart disease, enlargement of the heart, aortic insufficiency, mitral stenosis and insufficiency, left bundle branch block, angina pectoris.* A white married woman of 32 was referred to the Clinic on January 13, 1936, because of paroxysmal pain in the chest accompanied by severe dyspnea, orthopnea, palpitation, throbbing of the vessels of the neck, and profuse perspiration. Nine years earlier she had first been awakened at night with intense dyspnea and a sense of oppression in the chest, but no actual pain. The attack lasted 10 to 15 minutes. A second seizure occurred 5 nights later, and from then on the attacks increased steadily in frequency. With this progression, the sense of oppression was replaced by severe, stabbing pain which originated in the lower substernal region and radiated to both shoulders and at times down the inner aspect of both arms to the fingers. At the time of the patient's admission, attacks lasting 10 to 20 minutes were occurring 6 to 8 times each night, and occasionally a single seizure would persist for several hours. In addition, excitement often precipitated seizures during the day, but the attacks never were induced by exertion. Amyl nitrite was of only doubtful benefit, and the most helpful measures seemed to be sitting up or walking about. The patient had had rheumatic fever at the age of 8 years.

Physical examination revealed a greatly enlarged heart with regular rhythm and a rate of 102 per minute. A low-pitched diastolic murmur was heard at the aortic area and along the left border of the sternum. A harsh systolic and a loud diastolic murmur were present over the apex. There were no signs of congestive heart failure. The arterial blood pressure was 114 mm. systolic and 66 mm. diastolic.

Roentgenologic examination of the chest revealed great enlargement of the left ventricle and prominence of the pulmonary artery and conus. The electrocardiogram showed left bundle branch block and a normal *P-R* interval of 0.16 second. Mild hypochromic anemia was present. The Wassermann reaction of the blood was negative.

On October 29, 1936, the patient experienced an attack of severe pain accompanied by intense dyspnea and cyanosis and died within a few hours.

CASE 6.—*Rheumatic heart disease, enlargement of heart, aortic insufficiency and probable stenosis, mitral insufficiency and stenosis, angina pectoris, syphilis.* A white man of 25 came to the Clinic on February 14, 1938, because of attacks of severe, burning pain in the substernal region during the preceding 9 months. The seizures were induced by limited exertion and often came on during or soon after a meal. In addition, they frequently occurred at night, awakening him from sleep and forcing him to sit or stand or pace the floor. From its point of origin in the substernal region the pain usually radiated to the upper precordial area, and at times was accompanied by aching pain in the lower teeth. The attacks were accompanied by dyspnea, palpitation and profuse perspiration. Seizures occurred several times each day and a few times every night, and the pain usually lasted 20 minutes to 1 hour. The patient had had several attacks of rheumatic fever, but there had been no joint symptoms or signs since the age of 19 years. There was no history of luetic infection.

Physical examination revealed none of the stigmata of congenital syphilis. The temperature was normal, the pulse rate 72 per minute, and the blood pressure 120 mm. systolic and 20 mm. diastolic. The heart was moderately enlarged, and a rough systolic thrill was present over the base. Loud systolic and diastolic murmurs were heard at the aortic area and apex. The aortic second sound was absent. Capillary pulsation and Duroziez's sign were present, and the pulse wave was of the collapsing type. There were no signs of congestive heart failure.

The teleroentgenogram of the chest showed moderate enlargement of the left ventricle and prominence of the pulmonary artery and conus. A right

due to rheumatic aortic insufficiency is better than that of angina pectoris of effort due to coronary artery disease. In 3 of the 5 cases studied by Schwartz,¹⁰ the attacks spontaneously ceased to recur after a period of several months to 4 years. This apparently is unusual for it has not been reported by other observers. The experience recorded in the literature and in the present communication indicates that, although the average duration of life after the first attack of pain is greater in these patients than in those who have angina pectoris associated with coronary artery disease, the prognosis is uncertain in the individual case because of a distinct liability to sudden death. The other common cause of death is congestive heart failure.

Although amyl nitrite and nitroglycerin usually afford prompt relief from the seizures of angina of decubitus, there is no medical measure which is effective in preventing the development of the attacks. Surgical treatment, however, is often successful in this respect. The procedures employed have been paravertebral alcohol injection of the upper thoracic sympathetic ganglia, excision of the inferior cervical and upper dorsal sympathetic ganglia, and cervico-dorsal laminectomy with section of the posterior roots of the upper thoracic nerves bilaterally. Because no one observer has had the opportunity to study more than a small number of cases, no statement can be made concerning the relative value of these measures. It is of considerable interest that in the cases which Bland and White³ treated by paravertebral alcohol injection and in the case reported in the present communication treated by section of the posterior roots of the upper thoracic nerves, the vasomotor disturbances of the attacks were not altered even though the pain was partially or completely controlled.

Summary and Conclusions. 1. Six cases of angina pectoris of decubitus in young persons who had rheumatic heart disease with pronounced aortic insufficiency have been reported. All of the patients experienced repeated nocturnal attacks and it was of these seizures that they principally complained. In 4 of the 6 individuals, attacks also were induced by exertion. Prominent vasomotor changes such as flushing of the face, sweating, palpitation and throbbing of the vessels of the neck accompanied the pain in 5 patients. The pain in each case was similar in location, quality, and radiation to that of the common form of angina pectoris and usually was relieved promptly by amyl nitrite or nitroglycerin. In none of the cases was the initial occurrence of angina pectoris precipitated by active rheumatic infection.

2. The average duration of life after the first attack of angina pectoris due to aortic regurgitation is greater than in patients who have angina pectoris due to coronary artery disease, but the prognosis is uncertain in the individual case because of a distinct liability to sudden death.

anoxemia to produce anginal pain. In the case of angina pectoris of decubitus, however, some mechanism must be sought whereby, while the patient is at rest, the load upon the heart is increased to the point that the reduced coronary bloodflow is unable to maintain an adequate oxygen supply to the myocardium. The nature of this mechanism was revealed by the observations of Schwartz¹⁰ and Lewis.⁸ Schwartz¹⁰ noted that during the attacks of pain the blood pressure always was greatly increased above its usual level. In individuals who obtained relief from nitroglycerin or amyl nitrite, the relief was accompanied by a rapid reduction in the pressure, often to a level below the original value. If the pain returned after the effects of the drug had worn off, the recrudescence was accompanied by a rise in pressure to its former high level. Lewis⁸ demonstrated that the rise in blood pressure was accompanied by an increase in the pulse rate and that both of these changes preceded the onset of pain. Although these observations establish the fact that the attack of angina pectoris of decubitus is precipitated by a rise in blood pressure and pulse rate, it is often difficult to identify the factors which are responsible for these circulatory changes. In certain individuals there is a direct relationship to excitement or the taking of a meal,⁸ and it is probable that the nocturnal seizures are induced by factors which disturb the patient's sleep. MacWilliam⁹ demonstrated that disturbing dreams may cause a rise of as much as 70 mm. in the systolic blood pressure and an increase in pulse rate of 20 or more beats per minute. One of our patients was firmly of the opinion that dreams were responsible for her nocturnal attacks.

Bland and White³ reported 4 cases of the syndrome under discussion in which active rheumatic infection initiated the attacks. A similar relationship was present in 2 of the 8 cases recorded by White and Mudd¹⁴ while in a third, the attacks first developed after an attack of influenza. These cases, however, are exceptional, for in the great majority of instances of angina pectoris associated with rheumatic aortic insufficiency, there has been no relationship to active rheumatic infection. In none of the cases reported in the present communication was the initial occurrence of angina pectoris precipitated by active infection.

Although angina pectoris of decubitus in its pure form (the form in which there are no attacks related to exertion) is encountered most commonly in young individuals who have pronounced aortic regurgitation, it also occurs at times in older patients with rheumatic aortic insufficiency and in persons who have luetic aortitis with aortic insufficiency. More often, however, these older patients also suffer from attacks which are precipitated by exertion, possibly because of associated coronary artery disease or narrowing of the ostia of the coronary arteries.

There is general agreement that the prognosis of angina pectoris

BOOK REVIEWS AND NOTICES

LECTURES ON DISEASES OF CHILDREN. By SIR ROBERT HUTCHISON, BART., M.D., LL.D., F.R.C.P., Consulting Physician to the London Hospital and to the Hospital for Sick Children, Great Ormond Street, and ALAN MONCRIEFF, M.D., F.R.C.P., Physician to the Children's Department, Middlesex Hospital, and to Out-Patients, Hospital for Sick Children, Great Ormond Street; Pediatrician to Queen Charlotte's Maternity Hospital. Pp. 471; 107 illustrations. Eighth Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, \$6.75.

THE publication of an eighth edition of this little book indicates that it has been deservedly popular. It is not a complete text-book but is intended as a guide for the office and home practice of Pediatrics. As such, it would be helpful for practitioners and students. The lecture style makes it easily readable and the approach is always that of the office rather than the hospital. Many excellent photographs present vivid supplements to the descriptions in the text.

It is, therefore, unfortunate that the revision has not been drastic enough. To pick only a few examples: In the feeding schedules given for infants, diversified diets are introduced much later than is now recommended. In a book published in 1940, intramuscular blood should not be given as the preferred treatment for hemorrhagic disease of the newborn. Nor is the spleen enlarged in glycogen storage disease.

Books such as this one are needed but they must be accurate and embrace recent developments.

F. H.

BACILLARY AND RICKETTSIAL INFECTIONS, Acute and Chronic. A Text-book: Black Death to White Plague. By WILLIAM H. HOLMES, Professor of Medicine, Northwestern University Medical School, etc. Pp. 676. New York: The Macmillan Company, 1940. Price, \$6.00.

THIS book was written on the premise that teaching has two major functions: to transmit factual material and to point out the experiences and processes of observation, thought and experiment by which such factual material was evolved, and so perhaps to point the way to future progress. In short, teaching should teach not merely what to know, but how to think. Yet in medical teaching, partly because of the appalling mass of material involved, but partly also because of the attitude of teachers and the inadequacy of textbooks, there has been too much emphasis on so-called facts, with the result that thought is frozen and progress delayed. For the facts of today are so often the proven fallacies of tomorrow. In the words of the negro preacher, "it ain't so much the things you don't know, as the things you know, that ain't so, that gits you into trouble." Because of its masterful handling of the historical and evolutionary phases of the subject, as well as the broad view taken of the relation of disease and patient to the environment, this book deserves to be ranked as outstanding in excellence among current medical texts. It is all the more regrettable that the author's plan to write a second volume covering in a similar way the virus diseases and the infections of coecal, spirochetal, and protozoal etiology was ended by his untimely death. An inevitable disadvantage for students in so complete a text is its size: nearly four times that given the subject in the usual one-volume textbook of medicine, so that some might

3. There is no medical measure that is effective in preventing the occurrence of the attacks in this form of angina pectoris. Various surgical measures have been employed and often with considerable benefit. Because of limited experience, however, no statement can be made as to the relative value of the different procedures.
4. The earlier literature concerning this form of angina pectoris has been reviewed briefly, and the pathogenesis of the attacks has been discussed.

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CARDIAC CLASSICS. A Collection of Classic Works on the Heart and Circulation with Comprehensive Biographic Accounts of the Authors. (Fifty-five Contributions by Fifty-one Authors.) By FREDERICK A. WILLIUS, M.D., M.S. in Med., Chief, Section of Cardiology, The Mayo Clinic; Professor of Medicine, The Mayo Foundation for Medical Education and Research, The Graduate School, The University of Minnesota, and THOMAS E. KEYS, A.B., M.A., Reference Librarian, The Mayo Clinic; Formerly Carnegie Fellow, The Graduate Library School, The University of Chicago. Pp. 858; illustrated. St. Louis: The C. V. Mosby Company, 1941. Price, \$10.00.

THE growth of our knowledge of the circulatory system and its disorders is one of the most interesting and important topics in the history of medicine. It is quite appropriate, then, that an anthology on this subject be added to the bouquet of such productions, even though many of the items are already available in other collections. The authors have deliberately chosen to avoid all cardiac classics before Harvey's truly "epoch-making" contribution, but even so have filled a large book with the 55 masterpieces selected. *De gustibus non disputandum*, but one may at least record a slightly differing viewpoint: Still avoiding an undesirable, radical abridgment, some of the selections might well have been considerably shortened without material loss, and room then found for other noteworthy contributions, some of which are not found, supposedly because they happened to have antedated Harvey. Thus enough could be saved from Stephen Hales (27 pp.), Auenbrugger (23 pp.), Laennec (57 pp.), Austin Flint (29 pp.), Potain (26 pp.), and others to have found space for pertinent selections from Hippocrates, Galen, Leonardo, Vesalius, Canano, Servetus, Cesalpinus, Floyer, Willis, Hodgson, the brothers Weber, Purkinje, Pachon, Raynaud, Krogh and others of cardiovascular fame. Harvey, to be sure, should be premier in any selection of Cardiac Classics; but with many modern translations of *De Motu* now easily available, 63 pages might well seem too high a price to pay.

But again we recognize *de gustibus*, and are truly grateful for the excellent feast provided. Fifty-five masterpieces on the anatomy, physiology, pathology, semeiology, diagnosis and therapeusis of the cardiovascular system are presented in chronologic order from Harvey to James B. Herrick. Each is preceded by a brief biographic sketch and accompanied by well chosen, attractive illustrations.

We hope that this attractive volume will be successful in its aim of making medical men better acquainted with the great achievements of cardiology as described in the very words of the masters. E. K.

TEXTBOOK OF BACTERIOLOGY. By EDWIN O. JORDAN, PH.D., Late Andrew McLeish Distinguished Service Professor of Bacteriology, University of Chicago, and WILLIAM BURROWS, PH.D., Assistant Professor of Bacteriology, University of Chicago. Pp. 731; 170 illustrations. Thirteenth Edition, revised. Philadelphia: W. B. Saunders Company, 1941. Price, \$6.00.

THE change in the title from that of the twelfth edition, "A Textbook of General Bacteriology," indicates a trend in the book from general bacteriology towards medical bacteriology. The chapters on bacterial diseases of plants and bacteria in industry have been omitted, as well as the noticeable typographical errors and some of the obsolete material. The portions of the book dealing with the physiology of bacteria, the relation of bacteria to disease, immunity, viruses, and so forth have been expanded. It is to be regretted that in this revised edition such a lively subject as chemotherapy should be treated in the following manner and extent,

hesitate to recommend it as a beginner's text. But all would agree to its use by students for collateral reading. Every physician, whatever his special interest, who reads this book will profit in enjoyment and broadening of his viewpoint. That there be minor defects in a first edition is natural; none is serious and only one annoying: the persistent use of "tubercular" for "tuberculous."

It is to be hoped that the publishers will find someone sufficiently able and inspired to snatch up the torch that has fallen from the hand of Dr. Holmes.

R. K.

MEDICAL PROGRESS ANNUAL 1940. A Series of Fifty-two Reports Published During 1940 in The New England Journal of Medicine. Managing Editor: ROBERT N. NYE, M.D. Pp. 625; 9 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, \$4.00.

ACCORDING to the publisher's note, this volume "is an up-to-date guide to improvements in modern clinical medical procedures in a fairly large number of subjects of current interest."

The papers are arranged alphabetically according to title and are well chosen to present an interesting variety of medical and surgical subjects. An index is appended. Four of the fifty-two contributors apparently have no titular connection with the Harvard Medical School!

W. J.

A MANUAL OF ALLERGY. For General Practitioners. By MILTON B. COHEN, M.D., Director of The Asthma, Hay Fever and Allergy Foundation; Visiting Physician in Allergy, St. Alexis Hospital, Cleveland. Pp. 156. New York: Paul B. Hoeber, Inc., 1941. Price, \$2.00.

It is obvious that every family physician must be ready to recognize and treat allergic conditions. To gain this knowledge there are available to him an increasing number of books on allergy and the current textbooks on internal medicine. The former, written for those specializing in the field, are far too detailed and voluminous; the latter, written for medical students, are hopelessly inadequate. There is clearly a need for a text on allergy that shall be adequate but not too detailed for the general practitioner, and this need the author aims to fill. Opinions will differ, however, in regard to how much the practitioner needs to know, and so the Reviewer, while he agrees with nearly all that is said in the book and commands the excellence of the presentation, believes it to be decidedly inadequate in extent. But "too little" is an error that a second edition can correct far more readily than "too much."

R. K.

APPLIED PHARMACOLOGY. By A. J. CLARK, M.C., M.D., F.R.C.P., F.R.S., Professor of Materia Medica and Pharmacology in the University of Edinburgh; Formerly Professor of Pharmacology in the University of Cape Town, and Later in the University of London. Pp. 672; 91 illustrations, and 52 tables. Seventh Edition. Philadelphia: The Blakiston Company, 1941. Price, \$5.50.

In this revision one new chapter has been added to deal with the sulfonamide group of drugs, another to cover the pharmacology of the blood forming organs, and considerable changes have been made in the chapters on endocrines, vitamins, and immunology. Otherwise the book has not been greatly changed and the recent literature, particularly that on human pharmacology, is for the most part ignored.

C. S.

put into this magnum opus. It not only contains a vast amount of interesting reading for the moment, but should long remain a rich storehouse of reference for those searching in these fields.

E. K.

ESSENTIALS OF ELECTROCARDIOGRAPHY. For the Student and Practitioner of Medicine. By RICHARD ASHMAN, PH.D., Professor of Physiology, the Louisiana State University Medical Center; Director of the Heart Station, Charity Hospital of Louisiana, New Orleans, and EDGAR HULL, M.D., Professor of Medicine, Louisiana State University Medical School; Senior Visiting Physician, Charity Hospital of Louisiana, New Orleans. Pp. 373; 122 illustrations. Second Edition. New York: The Macmillan Company, 1941. Price, \$5.00.

THE second edition of this primer of electrocardiography retains its previous format. It has been expanded by 161 pages, with some amplification throughout, by the addition of a chapter on cardiac anatomy, and by appropriate discussion and illustration of chest leads.

W. J.

Clinical and Experimental Investigations on the GENITAL FUNCTIONS AND THEIR HORMONAL REGULATION. By BERNHARD ZONDEK. Pp. 264; 59 illustrations. Baltimore: The Williams & Wilkins Company, 1941. Price, \$4.50.

THIS small book describes the author's experiments in Jerusalem since 1935, and deals with estrogens in plants, effect of estrogens administered percutaneously, effects of long-continued estrogen administration, fate of estrogen, progesterone, and prolan in the body, influence of hormones on the menstrual cycle, and related subjects. The data are not of very general interest, but the book makes available in a concise form the author's recent views and investigations for those who are especially concerned with this phase of endocrinology.

I. Z.

FATAL PARTNERS: WAR AND DISEASE. By RALPH H. MAJOR, M.D. Pp. 342; illustrated. New York: Doubleday, Doran & Company, Inc., 1941. Price, \$3.50.

TWO, you might say three, of the Four Horsemen of the Apocalypse rage through these compelling pages. It is strange that we have so few books dealing directly with the peculiarly potent combination of war and disease, even though almost a quarter of a millenium ago Hippocrates announced his belief that a man who wished to know about medicine must of necessity follow the army. We welcome, then, this presentation by a competent and experienced medical historiographer, and especially at this time when much of the civilized world is already at war, with more still to come.

Not attempting a complete narrative of the "fatal partnership," the author has selected a dozen or more wars that illustrate the changing rôle of disease in warfare. He begins with the *Iliad* and the Peloponnesian War, in the latter of which the predominant rôle of the Plague of Athens in defeating the Athenians is stressed in a way that was never done in the schools I attended. The chapter on the Crusades gives good opportunity for a consideration of leprosy, scurvy and the noble work of the Knights Hospitalers. The "Gunpowder Era" introduces Paré; an earlier "War of Ideologies" is found in the Thirty Years' War; the debt of the "Corsican Colossus" to Larrey and Desgenettes provides another interesting chapter, as does the "Lady of the Lamp."

"Recent work, however, suggests that some of the sulfonamide dyes (sulfanilamides) may be efficacious in the treatment of infections with hemolytic streptococci and certain other organisms."
H. M.

A HISTORY OF MAGIC AND EXPERIMENTAL SCIENCE, Vols. 5 and 6, The Sixteenth Century (History of Science Society Publications, New Series IV). By LYNN THORNDIKE, Professor of History, Columbia University. Pp.: vol. 5, 695; vol. 6, 766. New York: Columbia University Press, 1941. Price, \$10.00 a set.

THESE two volumes conclude Professor Thorndike's extensive study of magic and experimental science from Roman times to the early years of the 17th century. Lest the title should seem to include two incongruous topics, it may be well to emphasize that the author interprets magic in the earlier sense represented by the Magi or wise men of Persia, that is, a mental attitude toward the world and not "merely a collection of rites and facts." The first pair of volumes, which appeared in 1923, carried the subject through the 13th century, the next pair covered the 14th and 15th centuries, this last pair deals with the 16th century.

As in previous volumes, Dr. Thorndike approaches nature from many angles. Lionardo and Achillini are followed by Cocles (chiromancy), Nifo (demons), Pomponazzi (incantations), Symphorien Champier, Agrippa, Melanchthon, and many others not to be found juxtaposed in other works. Chapters more familiar to physicians on Brasavola and pharmacy, and on German medicine (why German particularly?), are followed by others on alchemy, Vesalius, Fracastorius. Astronomy and astrology naturally demand and receive much space.

In a final chapter, the author's summary gives a good idea of the ground covered in these two, as well as in all six books of the series. In the two volumes under review we find that references were made to more than 3000 persons and to some 1700 topics and names of things. The influence of the humanism of the period under consideration is seen in the more frequent appearance of verse and orations in these volumes. Printers and publishers naturally become more prominent, with those of Venice in the lead, followed by Paris, Lyons and Rome; physicians of no fewer than 70 towns required notice. The topics most frequently included were animals, vegetables, and intellectual, religious and occult subjects, all but the first named being more frequent in these than in any of the previous volumes. More than one-third of the topics listed for the six volumes are found only in these two volumes. One is not surprised to find evidences of the Renaissance reaction against the outmoded Middle Ages, and of the tendency to seek for the hidden phenomena of nature rather than for the laws that govern them. Superstition, belief in witchcraft, intolerance, persecution, plagiarism were, to be sure, rife in the 16th century; but those who would look with pitying condescension on such benighted habits would do well to consider the more serious evil trends that have invaded much of the civilized world today and the storm clouds that threaten the very life of our intellectual world.

Not limited by restrictions of space, that are only too frequent in works of this kind, the author is able to lighten his theme with anecdotes and *obiter dicta*. The footnotes give ample evidence, as in previous volumes, of the wide range of Professor Thorndike's scholarship. It is indeed fortunate, also, that he was able to complete his consultation of European sources before the recent political upheavals rendered so many of them temporarily or permanently inaccessible.

One closes what is apparently to be the last volume of the series with a strong impression of the tremendous amount of careful work that has been

fare (M-14). By JOHN R. MOHLER, RAYMOND A. KELSER, and CASSIUS WAY. (Pp. 39. Price, 50c.) *Modern Aspects of the Antituberculosis Program* (M-15). By J. BURNS AMBERSON, KENDALL EMERSON, WILLIAM CHARLES WHITE, and LOUIS I. DUBLIN. (Pp. 38. Price, 50c.) *Chemotherapy* (M-16). By E. K. MARSHALL, JR., JOHN S. LOCKWOOD, and RENÉ J. DUBOS. (Pp. 42; 6 illustrations. Price, 50c.) *The University and Public Health Statesmanship* (M-17). By ARTHUR P. HUTCHENS, HARRY S. MUSTARD, WALLER S. LEATHERS, and CHARLES-EDWARD A. WINSLOW. (Pp. 33. Price, 50c.)

LIMITED space prevents a listing of titles and positions held by the authors, let alone a separate review of each pamphlet. Yet a glance at the subjects and the names of well-known authorities in many fields of medicine, dentistry and veterinary medicine, gives promise of an excellence of material and presentation that a perusal amply fulfills. We have here timely concise presentations of present knowledge and probable trends in fields of particularly active interest and importance, offered by those best qualified to do so. The many physicians who were privileged to attend the sessions of the Bicentennial Celebration will welcome this opportunity leisurely to read and digest the interesting and stimulating things they heard, and will join the Reviewer in enthusiastically recommending the whole series to all physicians.

R. K.

DISEASES OF THE NAILS. By V. PARDO-CASTELLO, M.D., Assistant Professor of Dermatology and Syphilology, University of Havana, etc. With a Foreword by HOWARD FOX, M.D., Professor of Dermatology and Syphilology, New York University, University and Bellevue Hospital Medical College. Pp. 193; 94 illustrations. Second Edition. Springfield, Ill.: Charles C Thomas, 1941. Price, \$3.50.

THIS excellent little handbook deserves a place on the desk of the practising physician, the diagnostician, and of course, by all means, the dermatologist. The second edition is materially improved over the first, in more extended consideration of the nail dystrophies associated with medical conditions; the photography is superior; the press work and half tone excellent; the bibliography up to date and inclusive. The book is a valuable contribution to an obscure field.

J. S.

TEMPERATURE—ITS MEASUREMENT AND CONTROL. By Numerous Authors. Sponsored by the American Institute of Physics. Pp. 1375; illustrated. New York: Reinhold Publishing Corporation. Price, \$11.00. Appendix of 25 reference tables is included and may be purchased separately bound for \$1.00 per copy.

THIS book is the record of a symposium held in New York, November 2, 3, and 4, 1939, under the auspices of the American Institute of Physics, and commemorating the 20th anniversary of a similar symposium on pyrometry. The chapter headings give an idea of the wide range of approach to the subject as afforded by 126 papers by several hundred of authors from many fields of pure and applied science: temperature and temperature scales; precision thermometry; education; natural sciences; temperature in biology; temperature and its regulation in man; automatic temperature regulation and recording; general engineering; metals and ceramics industries; oil industries; optical and radiation pyrometry; thermometric metals and alloys. The 12 papers by physicians represent only a small fraction of the whole volume, yet each presents a distinct contribution to the study of temperature. (It is hoped, however, that no reader

The latter half of the book is given over to Solferino, and the Red Cross, the Spanish American and South African Wars, the World War, and the preludes in Ethiopia and Spain to our present catastrophic condition.

This wisely selected material is embellished with adequate historical backgrounds and occasional pertinent anecdotes. The book should be interesting as well as informative to even the average lay reader and performs an important service for the thoughtful reader in determining the outcome of wars and in offering "a signpost for the future."

E. K.

ELECTROCARDIOGRAPHY. Including an Atlas of Electrocardiograms. By LOUIS N. KATZ, A.B., M.D., Director of Cardiovascular Research, Michael Reese Hospital; Assistant Professors of Physiology, University of Chicago. Pp. 580; 402 illustrations, including 806 electrocardiograms. Philadelphia: Lea & Febiger, 1941. Price, \$10.00.

This is probably the most inclusive textbook of electrocardiography yet to be written by an American author. A judicious balance has been struck in presenting fundamental concepts, illustrative tracings, and explanatory material. It is well suited to serve both as an introduction and a source of reference. Those interested in only a superficial knowledge of the subject will not care to read it. The author's originality in certain matters of classification and nomenclature will not be approved of by all cardiologists.

W. J.

UNIVERSITY OF PENNSYLVANIA BICENTENNIAL CONFERENCE PUBLICATIONS. There are now being published by the University of Pennsylvania Press, Philadelphia, in pamphlets ranging in price from 25c. to 75c., the addresses that were delivered on the occasion of the Bicentennial Celebration of the University in September, 1940. The pamphlets which have appeared are these:

- The Study of Man* (M-B). By LAWRENCE J. HENDERSON. (Pp. 22. Price, 25c.)
A Challenge to Scholarship (M-D). By W. MANSFIELD CLARK. (Pp. 20. Price, 50c.)
Problems and Trends in Virus Research (M1-2). By THOMAS M. RIVERS, WENDELL M. STANLEY, WILBUR A. SAWYER, THOMAS FRANCIS, JR., RICHARD E. SHOPE, JOSEPH STOKES, JR., and GEOFFREY RAKE. (Pp. 75. Price, 75c.)
Therapeutic Advances in Psychiatry (M-3). By EDWARD A. STRECKER. (Pp. 35. Price, 50c.)
Medical Problems of Old Age (M-4). By LOUIS I. DUBLIN, HOWARD T. KARSNER, O. H. PERRY PEPPER, and BARNEY BROOKS. (Pp. 46. Price, 50c.)
Nutrition (M-5). By CONRAD A. ELVEHJEM, CYRIL N. H. LONG and ELMER V. MCCOLLUM. (Pp. 46. Price, 50c.)
Female Sex Hormones (M6-7). By EDWARD A. DOISY, PHILIP E. SMITH, ROBERT T. FRANK, and ELMER L. SEVRINGHAUS. (Pp. 58. Price, 50c.)
Hypertension (M-8). By HARRY GOLDBLATT, EUGENE M. LANDIS and ALFRED W. ADSON. (Pp. 46. Price, 50c.)
Cause and Growth of Cancer (M9-10). By LOUIS F. FIESER, STANLEY P. REIMANN, PEYTON ROUS, WARREN H. LEWIS, MARGARET R. LEWIS, and BALDUIN LUCKÉ. (Pp. 64. Price, 75c.)
Dental Caries (M-11). By HENRY KLEIN, CARROLL E. PALMER, BASIL G. BIBBY, and ELMER V. MCCOLLUM. (Pp. 53; illustrated. Price, 50c.)
Development of Occlusion (M-12). By WILLIAM K. GREGORY, B. HOLLY BROADBENT, and MILO HELLMAN. (Pp. 72. Price, \$1.50.)
Problems of Intestinal Obstruction (M-13). By JOHN P. PETERS, OWEN H. WANGENSTEEN, W. OSLER ABBOTT, ALLEN O. WHIPPLE, and JOHN A. NELSON. (Pp. 56. Price, 50c.)
The Relation of Diseases in Lower Animals to Human Wel-

the undifferentiated character of the small lymphocytes, is accounted for by the undifferentiated leukoblasts which are found among the lymphocytes which have been used for these cultures. It is true that the authors state in their preface that they "have cited literature as it has seemed pertinent, not with any idea of completeness but always with the notion of enabling the reader to extend his acquaintance with the subject as he may choose. This method of selecting a bibliography may here and there do injustice, but in a subject still so unsettled, any other course would only add further prolixity to a literature already too copious." However, can we really clarify an issue if we ignore observations which do not fit in with our theory?

W. E.

THE CARE OF THE AGED (GERIATRICS). By MALFORD W. THEWLIS, M.D., Attending Specialist, General Medicine, United States Public Health Hospitals, New York City; Attending Physician, South County Hospital, Wakefield, R. I., etc. Pp. 579; 35 illustrations, 23 tables and 15 charts. Third edition, entirely rewritten. St. Louis: The C. V. Mosby Company, 1941. Price, \$6.00.

IN 1850 only 2.6% of the population of this country were 65 or more years old. By 1940 this percentage had risen to 6.3, and if present trends continue, it will reach 14.4 in 1980. Everyone who has practiced medicine for some time knows that the aged present many medical problems peculiar to their years. It would seem that an increasing attention should be paid, both in medical teaching and in practice, to the field of geriatrics. It is all the more surprising that, although 17 years have elapsed since the publication of the second edition of this work, it is still the only recent English text dealing with the medical care of the aged. The book therefore meets a real need and should find a wide appeal. While the style is often jerky, with sudden changes in the trend of thought, and there is much unnecessary repetition, the volume nevertheless offers a vast store of practical information that should make it very helpful to all, especially to young physicians.

R. K.

CEREBROSPINAL FEVER. By DENIS BRINTON, D.M. (OXON.), F.R.C.P. (LOND.), Physician in Charge of the Department for Nervous Diseases, St. Mary's Hospital, London; Assistant Physician to Out-Patients, National Hospital for Nervous Diseases, Queen Square, London, etc. Pp. 163; illustrated. Baltimore: The Williams & Wilkins Company, 1941. Price, \$3.00.

EPIDEMIC cerebrospinal fever is largely a disease of war time, when crowding, poor ventilation and winter colds set the stage for a rapid spread of infection. The early months of 1940 witnessed the largest outbreak that the United Kingdom has known. Whereas during the 4 years of the world war the average yearly number of cases was 2500, including both civilians and those in the services, there occurred over 5000 cases in the first quarter of 1940, or half as many in 3 months as in the 4 years, 1914 to 1918. Fortunately, a new and potent treatment was available, so that a new therapeutic triumph can be recorded, both as to mortality (23.7% among 4388 civilians, 11.3% among 705 non-civilians), and as to length of incapacity (3 weeks in hospital, 5 weeks of convalescence before return to active duty). This splendid little volume is based on the personal experiences of the author and on those of his colleagues in Britain. The emphasis is largely clinical, with detailed discussion of the problems of diagnosis; the dosage, mode of administration and toxic effects of the sulphonamides; the use of lumbar

will give any patient 10 *grams* of chloral hydrate at a dose, as stated in an obvious misprint.) For years to come, this volume should prove an interesting survey of today's knowledge on pyrometry as well as a valuable reference work.

R. K.

MANUAL OF THE DISEASES OF THE EYE. For Students and General Practitioners. By CHARLES H. MAY, M.D., Consulting Ophthalmologist to Bellevue, Mt. Sinai and French Hospitals, New York, etc. Pp. 519; 387 illustrations. Seventeenth edition, revised with the assistance of CHARLES A. PERERA, M.D., Associate in Ophthalmology, College of Physicians and Surgeons, Medical Department of Columbia University, New York, etc. Baltimore: William Wood and Company, 1941. Price, \$4.00.

THE 17th edition of this popular textbook appears just 2 years following the previous revision. The new edition has been revised and some parts rewritten; color plates and illustrations have been added and replaced. These changes have brought the contents up to date without any increase in size.

A new addition, of special interest at this time, gives the ocular requirements of the Army, Navy, Marine and Air services of the United States.

The many editions and 10 translations into foreign languages of this book set a remarkable record. It continues to be an excellent text for the undergraduate student and the general practitioner.

A. C.

LYMPHATICS, LYMPH, AND LYMPHOID TISSUE. Their Physiological and Clinical Significance. (Harvard University Monograph in Medicine and Public Health, No. 2.) By CECIL KENT DRINKER, M.D., D.Sc., Professor of Physiology, School of Public Health, Harvard University, and JOSEPH MENDEL YOFFEY, M.Sc., M.D., F.R.C.S. (ENG.), Senior Lecturer in Anatomy, University College of South Wales and Monmouthshire, Cardiff, Wales. Pp. 406; 50 illustrations. Cambridge, Mass.: Harvard University Press, 1941. Price, \$4.00.

THIS book is an important addition to the literature on the lymphatic system; it is superbly written and contains a bibliography covering 44 pages. In the first chapter the authors describe the anatomic and physiologic organization of the lymphatic apparatus. They then discuss the permeability of blood capillaries and its relation to lymph formation; the permeability of lymphatics; lymph flow and lymph pressure; the chemical composition and physical characteristics of lymph; the biologic significance of lymphoid tissue; the cell content of lymph; and the lymphocyte. The last chapter is devoted to a discussion of the rôle of the lymph and the lymphatic vessels in such conditions as edema, hypertension, shock, inflammation.

Though the authors give an excellent review of many features especially of the physiology of the lymph and the lymph vessels, other aspects, particularly anatomy and hematology, are not dealt with as profoundly. For instance, the authors do not give a clear picture of the cortical nodules of the lymph nodes; as a matter of fact, they present a diagram (Fig. 1) showing "cortical follicles" which do not exist. Moreover, in their chapter on the lymphocyte, they cite many facts and observations which seem to speak for the unitarian theory of leukopoiesis, while important data which are not in accord with this theory are not included. Thus, the maturation of the Golgi apparatus in the ripening lymphocyte is not mentioned; nor is it observed that the appearance of monocytes in tissue cultures of lymphocytes, which is regarded by many as the most important evidence for

The Therapeutics of Internal Diseases, Vols. 1 to 5. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D., David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. Associate Editor, ALBERT J. SULLIVAN, M.D., Chief Medical Officer, Gallinger Municipal Hospital, Washington, D. C. Pp. Vol. 1, 872; Vol. 2, 1042; Vol. 3, 738; Vol. 4, 791; Vol. 5, 765; all illustrated except Vol. 2. New York: D. Appleton-Century Company, 1940. Price, \$50.00 the set.

Wounds and Fractures. A Clinical Guide to Civil and Military Practice. By H. WINNETT ORR, M.D., F.A.C.S., Lincoln, Nebraska, Chief Surgeon, Nebraska Orthopedic Hospital. Pp. 227; 137 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, \$5.00.

Immunity Against Animal Parasites. By JAMES T. CULBERTSON, Assistant Professor of Bacteriology, College of Physicians and Surgeons, Columbia University. Pp. 274; illustrated. New York: Columbia University Press, 1941. Price, \$3.50.

The Baker Memorial, 1930-1939. A Study of the First Ten Years of a Unit for People of Moderate Means at the Massachusetts General Hospital. Pp. 75; 1 illustration. New York: The Commonwealth Fund, 1941.

Diseases of the Thyroid Gland. Presenting the Experience of More Than Forty Years. By ARTHUR E. HERTZLER, M.D., Surgeon to the Halstead Hospital; Professor of Surgery in the University of Kansas. Pp. 670; 354 illustrations and 2 colored plates. New York: Paul B. Hoeber, Inc., 1941. Price, \$8.50.

The Medical Clinics of North America, Vol. 25, No. 5, Boston Number, September, 1941. Pp. 330; 29 illustrations. Philadelphia: W. B. Saunders Company, 1941.

A Brief Course in Organic Chemistry. A Combined Textbook and Laboratory Manual. By REYNOLD C. FUSON, Professor of Chemistry in the University of Illinois, RALPH CONNOR, Associate Professor of Chemistry in the University of Pennsylvania, CHARLES C. PRICE, Assistant Professor of Chemistry in the University of Illinois, and H. R. SNYDER, Assistant Professor of Chemistry in the University of Illinois. Pp. 248; 24 illustrations. New York: John Wiley & Sons, Inc., 1941. Price, \$2.50.

The Essentials of Occupational Diseases. By JEWETT V. REED, B.S., M.D., F.A.C.S., and A. K. HARCOURT, B.S., M.D., Indianapolis, Indiana. Pp. 225. Springfield, Ill.: Charles C Thomas, 1941. Price, \$4.50.

Surgery of the Heart. By E. S. J. KING, M.D., M.S., D.Sc. (Melb.), F.R.C.S. (Eng.), F.R.A.C.S., Major A.A.M.C.; Honorary Surgeon to Out-Patients, Royal Melbourne Hospital; Jacksonian Prize-man, Royal College of Surgeons, etc. Pp. 728; 268 illustrations and 4 color plates. Baltimore: The Williams & Wilkins Company, 1941. Price, \$13.50.

NEW EDITION.

The Foot and Ankle. Their Injuries, Diseases, Deformities and Disabilities with Special Application to Military Practice. By PHILIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Professor of Orthopaedic Surgery, Post-Graduate Medical School of Cook County Hospital, etc. Pp. 665; 304 illustrations. Second Edition; 304 Line Drawings by HAROLD LAUFMAN, M.D. Philadelphia: Lea & Febiger, 1941. Price, \$9.00.

puncture (now limited to the diagnostic puncture, the final puncture to make sure the cerebrospinal fluid has returned to normal, and an occasional additional puncture for the treatment of headache or pains in the back and neck); nursing care; prognosis (emphasis on early diagnosis, which together with increased mortality in infants and the aged, explains the difference between civilian and non-civilian mortality). The book should be read at once by all physicians who are likely to encounter cases of this disease. R. K.

MICROBES WHICH HELP OR DESTROY US. By PAUL W. ALLEN, PH.D., Professor of Bacteriology and Head of the Department, University of Tennessee, D. FRANK HOLTMAN, PH.D., Associate Professor of Bacteriology, University of Tennessee, and LOUISE ALLEN McBEE, M.S., Formerly Assistant in Bacteriology, University of Tennessee. Pp. 540; 102 illustrations, and 13 color plates. St. Louis: The C. V. Mosby Co., 1941. Price, \$3.50.

THIS book is a successful attempt to make the layman "microbe conscious" and at the same time, perhaps unintentionally, the authors have presented us with a work which could be used to good advantage as a textbook for general biology in colleges. The material is well organized, clearly presented and easily readable, being, for one thing, printed on eye-ease paper. The authors briefly discuss the history of bacteriology, the relationship of science to man's well-being, the nature of microbes, and most of the specific infectious diseases of man, whether of bacterial, viral or rickettsial origin. Fungi and protozoan parasites are also included. Other more general subjects considered are: infection and resistance, disinfection, community health activities, making drinking water safe, milk and milk products, disposal of sewage, garbage and wastes, the importance of microbes to surgeons, appendicitis, tooth infections, conjunctivitis, food poisoning, various fermented foods and essential industrial products. H. M.

NEW BOOKS.

National Research Council. Report of Committee on Drug Addiction 1929-1941 and Collected Reprints 1930-1941. Pp. 1581; illustrated. Washington, D. C.: National Research Council, 1941.

The New International Clinics, Vol. 3 N.S. 4, 1941. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia, with 17 Collaborators. Pp. 300; illustrated. Philadelphia: J. B. Lippincott Company, 1941.

This volume presents 9 original contributions of varied nature and 13 "clinics" from Washington University. Dr. Cantarow reviews recent advances in clinical biochemistry.

Hypoparathyroidism in Denmark. A Clinical Study. By AAGE LACHMANN. Pp. 269; illustrated. Copenhagen: Einar Munksgaard, 1941. Price, Dan. Cr. 12.

Sulfanilamide and Related Compounds in General Practice. By WESLEY W. SPINK, M.D., Associate Professor of Medicine, University of Minnesota Medical School. Pp. 256. Chicago: The Year Book Publishers, Inc., 1941. Price, \$3.00.

The Furtherance of Medical Research. By ALAN GREGG, M.D., Director for the Medical Sciences at the Rockefeller Foundation. Pp. 129. New Haven: Yale University Press, 1941. Price, \$2.00.

when given by this route, judging from the percentage of ingested drug that is recovered in the urine. After single doses, from 40% to 90% of the latter drug appears in the urine.^{19a, b, 57, 66, 70, 104, 117, 118} Brown *et al.* recovered 85% of all the administered sulfapyridine from the urine of one of their patients who was treated with this drug for 11 days, but this patient received intramuscular as well as oral doses.^{19a} Kinsman *et al.*, on the other hand, were able to recover from the urine less than 30% of the total drug administered to patients who were under continuous treatment with 4-hourly doses of sulfapyridine.⁵⁷ Orally administered sulfathiazole and sulfadiazine occupy an intermediate position; they are usually recovered from the urine more completely than sulfapyridine but not so well as sulfanilamide.^{67, 83, 84, 95, 97, 101, 102, 118} The percentage of orally administered sulfaguanidine that is recovered from the urine is variable, but is usually quite low.⁷³ Urinary recoveries after ingestion of any of the drugs may vary considerably in different individuals. It also seems likely that such recoveries are more complete after a single dose than they are after repeated doses or during continuous administration of the drugs. Parenterally administered sodium salts are excreted almost quantitatively.^{83, 87a, 118}

Renal clearances of the sulfonamide drugs have been studied in experimental animals and in humans. Marshall *et al.*^{72a} compared the renal clearances of sulfanilamide with the simultaneously determined creatinine clearances in dogs. They found the sulfanilamide clearance to be 20% to 30% of the creatinine clearance, indicating tubular reabsorption of 70% to 80% of the sulfanilamide. The findings in man were very similar. They also stated that the acetyl form is cleared more rapidly than the free form. Stewart *et al.*¹¹⁶ arrived at the same conclusions in calculating the sulfanilamide clearances in a number of patients 6 hours after the last therapeutic dose. These findings have also been confirmed by others.^{40, 46}

Marshall and Litchfield⁷⁰ repeated the clearance studies, using sulfapyridine, and obtained results similar to those with sulfanilamide (16% to 39% of the simultaneous creatinine clearance). It is concluded that sulfapyridine is excreted more slowly than sulfanilamide and its excretion is usually not complete even after 3 to 4 days. The conjugated sulfapyridine often persists in the blood for some time after the free form of this drug can no longer be detected.^{104, 117, 118}

Sulfathiazole is excreted rapidly^{40, 67, 96, 118} and the clearance of its acetyl derivative is usually greater than that of the free form. Sulfadiazine is excreted more slowly than any of the other three drugs that have been considered.^{83, 84, 97, 102} When the renal function is normal, the conjugated sulfathiazole and sulfadiazine fractions are probably cleared more rapidly than the unconjugated ones, since the former often disappear from the blood before the latter. In this respect, sulfathiazole and sulfadiazine seem to differ from sulfanilamide and sulfapyridine.

The higher clearance rates of the acetyl derivatives of sulfanilamide and sulfapyridine, as compared with their free forms, hardly seem compatible with the observation that the conjugated forms of the drugs are found in the blood for some time after the free drugs can no longer be detected. However, since the levels of the conjugated drugs upon which these computations of the clearance are based are usually quite small, they lend themselves to large errors. Furthermore, determina-

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS.

UNDER THE CHARGE OF

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THE URINARY TRACT IN SULFONAMIDE THERAPY.

THREE important aspects of sulfonamide therapy, all of which concern the urinary tract, will be considered in this review. These are: 1, the excretion of the sulfonamide drugs; 2, the urinary complications of sulfonamide therapy; and 3, the sulfonamide treatment of urinary tract infections. The first of these is the most fundamental, since the two latter phases of sulfonamide therapy are dependent upon the manner in which these drugs are excreted into the urine. For the most part, only those drugs will be considered which have been accepted as effective and have come into wide use in this country, namely, sulfanilamide, sulfapyridine and sulfathiazole. The more recently accepted drugs, sulfaguanidine and sulfadiazine, will also be considered.

Absorption and Excretion of Sulfonamides. The sulfonamide drugs occupy a unique place in the therapy of disease. They are given in large, repeated doses. They are sparingly soluble, yet well absorbed. In the body they are partly converted to the para-acetyl derivatives, which are less soluble and usually less active and more toxic than the parent compounds. They are excreted in both the free and the acetylated forms and probably also as other conjugated derivatives.¹⁰⁷

The various sulfanilamide derivatives are absorbed to different degrees from the gastro-intestinal tract.⁷⁰ In the case of each of the sulfonamides, however, almost all of the absorbed drug, regardless of the route of administration, is excreted into the urine. Only small quantities are excreted in the tears, saliva, breast milk and stools, or through the skin.^{2,20,23,53}

Sulfanilamide is recovered almost quantitatively after oral administration.^{68,72a,b,116,118} Sulfapyridine is absorbed much less completely

Reinhold *et al.*,⁹⁶ in a study of 14 patients on continuous doses of sulfathiazole, found oliguria in 3, hyposthenuria in 6 and depression of the urea clearance in 6 patients to as much as 50 % of the mean normal. They observed that the change was transitory, since in the majority of patients there was a return to normal while they were still receiving sulfathiazole. These authors do not feel that the renal depression is ascribable to sulfathiazole *per se*. Climenko *et al.*²⁵ produced a marked depression of urea clearance and of phenolsulphonphthalein excretion with an elevation in blood non-protein nitrogen in some of their dogs on large doses of sulfathiazole (150 to 250 mg. per kilo of body weight). These changes were temporary and normal renal function was reestablished quickly when the drug was discontinued. Toomey¹²³ stressed the danger of urinary retention in expediting the precipitation of acetyl sulfapyridine and the formation of uroliths.

Solubility. Allport⁶ studied the solubility of sulfanilamide in water in relation to temperature. He found this drug to be soluble to 1 part in 240 (0.42 %) at 15° C. and to slightly more than 1 % at body temperature. At higher temperatures the solubility increased markedly. Marshall *et al.*⁷³ give the solubility of the free drug as 1.48 % at 37.5° C. and at pH 7.1, and the acetylated form as 0.534 % under similar conditions.

Sunderman and Pepper¹²¹ showed that sulfathiazole and its acetyl derivative are more soluble in alkaline urine, at pH 7.5 or higher, than in acid urine. The acetyl sulfathiazole is much less soluble than the free form. The increased solubility of the acetyl sulfathiazole in alkaline solution, however, does not seem to be of sufficient magnitude to be of clinical significance, although these authors advise alkalization of the urine to prevent complication in the course of therapy.

Marshall *et al.*⁷³ and Feinstone *et al.*³⁵ have presented the solubilities of a number of common sulfonamides in water and in urine. Some of the important solubilities adapted from their combined data may be summarized in tabular form.

TABLE I.—SOLUBILITY OF SULFONAMIDE COMPOUNDS.

Drug	Solubility in mg per 100 cc		pH.	Temperature (°C.).
	In water.	In urine.		
Sulfanilamide	1480		7 1	37 5
Acetyl sulfanilamide*	534		7 1	37 5
Sulfaguanidine	220	218	7 1	37 5
Acetyl sulfaguanidine	40	48	7 1	37 5
Sulfapyridine	54	57	7 1	37 5
Acetyl sulfapyridine	16	19	7 1	37 5
Acetyl sulfapyridine		23-31	6 9	37 0
Acetyl sulfapyridine		30-34	6 3	37 0
Sulfathiazole	96	..	7 1	37 5
Acetyl sulfathiazole	6	.	7 1	37 5
Acetyl sulfathiazole		26-38	6 3	37 0
Sulfadiazine	12	32	6 6	37 0
Acetyl sulfadiazine	15	85-88	6 9	37 0
Acetyl sulfadiazine		115	6 3	37 0

* The acetyl compounds are all N-acetyl derivatives.

When the figures given for solubilities of free and acetylated sulfonamide drugs, based on the experimental studies already mentioned, are

tions of drug clearances after oral administration^{72a,116,118} may not be very reliable because of the variable and irregular absorption of the drugs from the gastro-intestinal tract.

A number of other drugs that have not come into common use have also been investigated. Alyea *et al.*⁸ found that disulfanilamide was absorbed and excreted by the normal kidney more slowly than sulfanilamide, but the sodium salt of the former was excreted much like sulfanilamide. Sulfamethylthiazole is absorbed and excreted slowly.^{40,118} Glucose-sulfapyridine is excreted much more rapidly than sodium sulfapyridine after parenteral administration, but after oral administration its absorption and excretion are considerably delayed.^{37,122} Prontosil is excreted very rapidly, 85% to 95% of a single dose being recovered in the urine within 5 hours.¹⁰⁰

Effect of Diuresis. There is some disagreement concerning the effect of diuresis on the excretion of sulfanilamide. Marshall^{72a} found that diuresis increased the clearance rates of sulfanilamide in dogs and Stewart *et al.*¹¹⁶ confirmed this finding in man. Alyea *et al.*,⁸ on the other hand, found that the total quantity of sulfanilamide excreted over a given period was constant regardless of the urinary output. They found high sulfanilamide levels in concentrated urines and low levels in dilute urine. The results with sulfanilyl-sulfanilamide were the same. Lucas and Mitchell⁶⁸ did not believe that diuresis increased the elimination of sulfanilamide, but their data are based on studies in a single patient.

Sulfapyridine is apparently excreted at a more constant rate irrespective of the volume of urinary flow.²⁰ This is probably true also of the other common compounds, except sulfanilamide.

Effect on Renal Function. The effect of high blood levels on renal function was studied by Marshall *et al.*^{71,72a} in dogs. They found that large oral doses of sulfanilamide depressed the creatinine clearance for several hours, and large intravenous doses (2 gm. per kilo) produced a marked decrease in the urine flow and in the creatinine clearance that lasted for 6 hours, but there was complete recovery in 24 hours. Molitor and Robinson,⁷⁷ on the other hand, found no evidence of renal damage in rats fed large doses of sulfanilamide for 10 days. They studied the urinary output and the ability to concentrate urine.

Alyea *et al.*⁸ correlated the ability to excrete sulfanilamide with the excretion of intravenously administered phenolsulphonphthalein. They gave patients 1 gm. of sulfanilamide daily for every 10% of intravenously injected phenolsulphonphthalein recovered from the urine in the first half hour. They found that they could thus maintain a constant level of 3 to 4 mg. per 100 cc. of the drug in the blood. In 1 patient they measured the sulfanilamide excretion of each kidney separately and found that a normal kidney was able to excrete 852 mg. of sulfanilamide in 7 hours, while the other kidney excreted only 43 mg. in the same period. The difference in the phenolsulphonphthalein excretion of these kidneys was comparable with that of the sulfanilamide excretion.

With sulfapyridine, Marshall and Litchfield⁷⁰ found that the very high blood levels (38 to 45 mg. per 100 cc.) attained following intravenous injection of the sodium salt depressed the creatinine clearances slightly. They state that this drug appears to cause no more depression of renal function than does sulfanilamide.

not all, of this gave a reaction for iron and presumably resulted from changed blood.

Antopol and Robinson^{10a} found urolith formation in 2 of 300 rats who had been given large daily doses of sulfanilamide. Hawking⁴⁷ found large numbers of crystals "which resembled those of sulfanilamide" in the urine of rabbits after single large intraperitoneal doses. He found no renal lesions in these animals. Oakley,⁸⁰ however, observed calculi of prontosil dye in the kidneys of mice following the administration of large single doses or of repeated small doses of this drug. These calculi gave rise to obstruction with dilatation of the straight and convoluted tubules. The death of many of these mice was attributed to renal failure resulting from this obstruction. Stewart *et al.*¹¹⁶ reported a unique experience in a patient in whom precipitation of acetyl sulfanilamide crystals occurred in an indwelling catheter during the collection of urine for clearance determination.

Nelson⁷⁹ administered di-sulfanilamide to rabbits and found degenerative changes in the kidneys, with dilatation of the tubules which contained some crystalline material that may have been precipitated drug. Similar changes were noted after sulfanilamide, but these were only slight or moderate in degree. Sulfanilamide crystals were observed in the collecting tubules, but these were fewer than with di-sulfanilamide. In hens, he could demonstrate only very slight renal change from toxic doses of sulfanilamide.

From the course of events in some cases of acute hemolytic anemia resulting from sulfanilamide therapy, one might expect to see pathologic changes in the kidney similar to those observed in fatal cases of blackwater fever or after hemolytic reactions that follow transfusions. Such findings have indeed been reported in one case,¹³⁵ in which plugs of precipitated hemoglobin were seen in the kidney tubules and death resulted from renal failure. We have also seen a case of delayed death from uremia following acute hemolytic anemia that occurred in the course of sulfanilamide therapy. Myers and Rom⁷⁸ reported a case of acute hemolytic anemia with hemoglobinuria, uremia and anasarca after 460 gr. of sulfanilamide given over a period of 60 hours. Their patient made a complete recovery. Spring and Bernstein¹¹⁵ reported 2 such cases, in each of which they mention the occurrence of renal damage, but they present little evidence to indicate that such damage occurred. Their patients had minor and transient elevation of blood urea nitrogen. Koletsky⁶⁰ noted no specific changes at autopsy in a case of hemolytic anemia resulting from sulfanilamide. In this case, he observed clumps of yellowish-brown material in the collecting tubules, but these did not give a reaction for iron.

Changes in the kidney due to the direct action of sulfanilamide or its acetyl derivative must be extremely rare, if they occur at all. This is probably due to the relatively high solubility of these compounds in the urine of patients under treatment.

Sulfapyridine. In marked contrast to sulfanilamide, which produces little or no change in the kidney, sulfapyridine produces the major share of its toxic effects in this organ. It is of interest that Wien,¹³² the first to investigate the toxicology of sulfapyridine, found no renal damage, but he used small doses. Crystalluria was recognized early by Stokinger.¹¹⁷ Shortly thereafter, Gross *et al.*^{44,45} and Antopol and

compared with the much higher concentrations actually found in the urine of many patients under therapy,^{8,20,27,83} it becomes obvious at once that other factors must come into play. A few observations have been made which serve to explain this discrepancy, at least in part.

Curtis and Sorbin²⁸ investigated the solubility of acetyl sulfapyridine in urine and found that it increases with increasing specific gravity of the urine. They suggested that the solubility may vary with the urea content. Their preliminary studies with acetyl sulfathiazole indicated that the solubility of this drug is similar to that of sulfapyridine.

Scudi *et al.*¹⁰⁷ isolated from urine a diazotizable derivative of sulfapyridine which was present in concentrations far above the known *in vitro* solubilities of the free drug or of its acetyl form. They considered that this soluble compound might be a glucuronate of sulfapyridine^{20,107} and were able to demonstrate a markedly increased glucuronate excretion on a controlled diet in normal males, and in pneumonia patients following ingestion of sulfapyridine.

Concentration of Sulfonamides in the Kidney. Animal experiments have indicated that sulfanilamide is distributed more or less evenly in the various tissues,^{72a} while sulfapyridine, sulfathiazole and sulfadiazine are distributed somewhat unevenly.^{24,70} In patients treated with sulfapyridine Brown *et al.*^{19a} found the concentration of the drug in the kidney to be much higher than in other organs. Other studies from our laboratory^{83,118} have indicated that, in patients dying while under sulfonamide therapy, the concentration of drug in the kidney of those who had received sulfanilamide is the same as in the blood and other organs. It was considerably higher in the kidney than in the blood and other organs in those who had been given sulfapyridine or sulfathiazole. A large proportion of the additional amounts were found to be in the conjugated form. In most of the kidneys from fatal sulfadiazine treated patients the concentration of drug was the same as in the blood, thus resembling sulfanilamide, but in one isolated case a much higher level was found in the kidney. While the concentrations of various drugs in the kidney may be influenced by contamination with urine,^{19a} these findings are nevertheless of interest in view of the greater tendency of renal complications to occur with sulfapyridine and sulfathiazole, as compared with sulfanilamide and sulfadiazine.

Pathologic Changes in the Urinary Tract Resulting From Administration of Sulfonamide Drugs. *Sulfanilamide.* Direct renal damage resulting from sulfanilamide administration is quite rare and it is certainly less frequent than with any of the other drugs with which we are concerned in actual therapy. Domagk,³⁰ in his first report on prontosil in mice, noted that it produced no pathologic elements in the urine. Marshall *et al.*⁷¹ reported a similar absence of abnormal urinary findings in dogs receiving large doses of sulfanilamide (0.1 to 0.2 gm. per kilo daily) for several months. These animals had normal kidneys at autopsy. A very large single dose (2 gm. per kilo) produced minimal pathologic changes in the collecting and Henle's loop tubules. Mice dying as a result of large doses of sulfanilamide and acetyl sulfanilamide were found to have normal kidneys.

Molitor and Robinson,⁷⁷ in studies on chronic toxicity of sulfanilamide in rats, found considerable collections of granular brown pigment in the convoluted tubules and occasional brownish casts. Much, but

Renal complications are generally considered to be more frequent under sulfapyridine therapy than with any other common sulfonamide. Gross *et al.*⁴⁵ collected from the literature reports of 128 cases of hematuria resulting from sulfapyridine, with uroliths specifically mentioned in 7 cases. Renal complications are also frequent in infants and in children.^{51, 98 106 110 130 134} The incidence of hematuria varies from less than 1% to as high as 40%.^{9 13 196 43 51 55, 82 99} The latter figure is from Antopol's series of 40 sulfapyridine-treated pneumonia patients.⁹ Crystalluria is even more frequent, but, by itself, it is probably not significant. In most series, the incidence of urinary complications is between 5% and 10%. There are a few observations which indicate that the renal damage resulting from therapeutic doses is usually not permanent.^{196 51}

MacLeod⁶⁹ noted that renal function may be depressed during sulfapyridine treatment without the appearance of hematuria. In 2 patients treated with this drug he observed a temporary depression of the urea clearance to critical levels associated with azotemia, although hematuria was absent in either instance. He also found that acute hemorrhagic Bright's disease developed in 2 other patients with pneumonia who received this drug. Both of these patients recovered from the acute phase, one apparently completely, but in the other case only partial recovery took place during 4 months following the onset of the nephritis.

Eldahl³³ reported a series of 55 patients treated with acetyl sulfapyridine in which only 1 case of hematuria was noted. The compound he used was probably the N₁-acetyl derivative, which is an active compound, and not the para-acetyl derivative, which is the form that is excreted in the urine in patients treated with sulfapyridine and which is inactive. Brown *et al.*¹⁹⁶ and Plummer and McLellan⁸⁵ showed that the calculi formed by precipitation of the latter are not radio-opaque.

Ravid and Chesner⁹⁵ reported a case of anuria that resulted from a hemoglobin precipitate in the renal tubules resulting from hemolytic anemia caused by sulfapyridine. Tragerman and Goto¹²⁴ reported a similar case. Since acute hemolytic anemia is much less frequent with sulfapyridine as compared with sulfanilamide, renal damage from this mechanism is correspondingly rare.

Sulfathiazole. Renal change resulting from administration of this drug may be much the same as that produced by sulfapyridine.^{1 45 52 63 91 126 131} Rake *et al.*⁹² showed this in rats, although sulfathiazole was less toxic for these animals than was sulfapyridine. They believe that both drugs produce primary damage to the glomeruli and tubules which is independent of the mechanical obstruction. Gross *et al.*⁴⁵ found acetyl sulfathiazole precipitated in the collecting tubules and occasionally in the convoluted tubules. Lehr *et al.*⁶² reported finding a precipitate of free sulfathiazole in the kidneys of rats and mice after massive single doses of the drug. In animals that died quickly the drug was found in the renal tubules and papillary ducts, but in those that lived longer the precipitate was found successively in the ureters and in the bladder.

Horack⁵² and Pepper and Horack⁵¹ described the kidneys of a patient who died after a period of anuria while on sulfathiazole treatment. They saw gritty deposits in the collecting tubules, and the pelvis of each kidney was hemorrhagic and thickened and filled with gritty

Robinson^{10a,b} recognized urinary obstruction from drug calculi in experimental animals. The former workers analyzed the crystalline material obtained from the urinary tract and found it to consist largely of the acetyl form of sulfapyridine. Almost simultaneously there appeared reports by Lawrence⁶¹ and by Southworth and Cooke¹¹² of 3 cases of hematuria associated with sulfapyridine therapy in man. In these cases there was renal colic and nitrogen retention.

There have been numerous subsequent reports on renal change in both experimental animals and man, as well as numerous case reports of sulfapyridine oliguria and anuria.^{3,11,19a,b,22,31,41,61,67,69,99,103,108,110-112,124,125,134} The clinical picture has been described many times and is now generally recognized. Hematuria is one of the chief symptoms and may or may not precede oliguria. Anuria may appear suddenly or after a short period of oliguria. It may appear early or late in the course of drug administration, or even after the drug has been stopped.¹¹¹ If any urine is passed, it usually is grossly bloody and contains large amounts of crystalline material which can usually be shown to be mostly acetyl sulfapyridine.⁴⁴ Renal or ureteral pain is marked. Stopping the drug and forcing fluids may relieve the symptoms rapidly and completely, but ureteral catheterization and lavage are often necessary. Drug retention occurs and acetylation usually becomes marked under these conditions. The non-protein nitrogen may rise progressively unless the obstruction is relieved and the urine flow reestablished. The condition may be unilateral, in which case there is no nitrogen or drug retention. The blood pressure is usually not elevated unless there is complete kidney shut-down.

The pathologic changes in the urinary tract produced by sulfapyridine are mainly the result of the precipitation of acetyl sulfapyridine in the urinary tract. The lesions may be unilateral or bilateral. The earliest lesions consist of the aggregation of crystals with blood and amorphous material, anywhere along the urinary tract. These may give rise to obstruction of the urinary flow. The ureters and pelvis become dilated and thinned and the kidneys become enlarged and edematous. Hemorrhagic ureteritis and pyelitis occur with periureteral inflammatory changes. The renal pelvis is often filled with gross aggregates of crystals, amorphous material, fibrin and blood, and these may extend upward into the papillary ducts. The kidney tubules may show varying degrees of dilatation and epithelial degeneration with intertubular collections of leukocytes. The glomeruli may also be affected and the glomerular spaces may be enlarged. The distended tubules are often visible grossly in the cut section of the kidney, and appear as striations radiating from the pelvis.^{10a,b,19a,85,87b,92,103,119,123,125,126}

The high concentration of sulfapyridine in the kidney, as compared with blood and other organs, has already been noted. These levels may be particularly high in those who die as a result of renal failure. In such cases, the percentage of drug found in the kidney as the acetyl derivative is usually very high, particularly if the last dose was given some time before death occurred.

Sulfapyridine may also produce primary parenchymal renal damage that is not a result of precipitated crystals or obstruction.^{10a,b,92} Occasionally thrombi are found in the kidney veins, and obliterating lesions are seen in the lumens of veins that are not close to inflammatory zones.⁹²

plications are more common in an acid urine. Wilson and Billingsley¹³⁴ and Sadusk *et al.*¹⁰³ have obtained alkaline urine by cystoscopy from the renal pelvis of patients who were suffering from sulfapyridine urolithiasis. The greater solubility of the acetyl derivative in alkaline solutions has already been mentioned. It is probably beyond the capacity of the human kidney to excrete urine which is sufficiently alkaline to increase significantly the solubility of the acetyl compounds.

Excretion of Sulfonamides in Patients With Reduced Renal Function. Lucas and Mitchell⁶⁸ noted that in the presence of impaired renal function, the blood concentration of sulfanilamide rises rapidly and, when the renal dysfunction is marked, very high levels can result from small doses. Long⁶⁵ noted that an anuric patient maintained a constant blood level for 1 week after a single dose of sulfanilamide. We have observed a patient who maintained a high sulfapyridine level in the blood for a whole month after his last dose of drug. In this patient there was a rising level of blood non-protein nitrogen, increasing edema and rising blood pressure. The percentage of circulating sulfapyridine which was in the conjugated form increased progressively so that after 3 days, about two-thirds of the drug was found in the blood in that form. Allen⁵ reported a case with marked sulfanilamide retention and excessive acetylation accompanying nitrogen retention. Strauss *et al.*¹¹⁸ found that patients who had elevated blood non-protein nitrogen values before death had, at autopsy, high concentrations of drug in the cardiac blood with large proportions of it in conjugated form. Reinhold *et al.*⁹⁶ state that the clearance of both sulfathiazole and acetyl sulfathiazole is reduced in the presence of impaired renal function. Sulfadiazine is probably tolerated by the damaged kidney better than either sulfapyridine or sulfathiazole. Long^{64b,c} noted that in the face of grave kidney damage, the free and conjugated fractions of sulfadiazine seem to be more readily excreted by the damaged kidney than is usually the case with sulfapyridine or sulfathiazole, and this corresponds with our experience.³⁸

Use of Sulfonamides in the Treatment of Urinary Tract Infections. Prontosil. Soon after the discovery of prontosil by Domagk, its value as a urinary antiseptic was appreciated. Huber⁵⁴ used it with excellent results in the treatment of colon bacillus pyuria in 14 children and ascribed its first use in this condition to Temming, but noted that the latter failed to study the bacteriology of his cases.

The use of sulfanilamide was soon taken up in England by Kenny *et al.*⁵⁶ and in this country by Helmholtz.^{43a} It was found to be extremely valuable in the treatment of pyelitis of pregnancy^{15,17,88} and rendered largely unnecessary the former practices of acidification and alkalinization, ureteral drainage and the occasional resort to therapeutic abortion.

Many authors have reported successes in the treatment of acute colon bacillus infections of the urinary tract.^{7,15,17,26,34,42,48a,50,83,93,94,109,120,127,128} It soon became apparent, however, that although the colon bacillus was eradicated, some other organisms remained unaffected. Staphylococcus, however, was generally found to be susceptible.^{48a,50,83,94,109,120,127} Barer¹⁶ reported a cure of typhoid bacilluria with sulfanilamide.

Strep. faecalis is generally regarded^{26,48a,49,75,76} as resistant to sulfanilamide. Bliss and Long¹³ found that beta hemolytic streptococci belonging to Group D were resistant in several patients. They also tested a number of strains *in vitro* and found them all resistant to this drug.

material. Loewenberg *et al.*⁶³ found calculi in the collecting tubules of the kidney, in the ureters and in the bladder of a patient who died during sulfathiazole treatment.

Spink and Hansen¹¹⁴ encountered nitrogen retention with oliguria once and gross hematuria once among 100 sulfathiazole-treated cases. Others have encountered these complications in about the same frequency.^{39,41,96,129,130} Garvin,⁴¹ however, noted hematuria in 14% of sulfathiazole-treated cases, as compared with 10% of those receiving sulfapyridine, but he gave as much as 10 gm. of sulfathiazole daily in an attempt to attain blood levels comparable with those found in patients receiving 5 gm. of sulfapyridine daily. He noted crystalluria in 61% of patients treated with sulfathiazole and in 28% of those treated with sulfapyridine. The differences are understandable in the light of the larger doses of the former, as well as its more rapid excretion into the urine. Anuria and oliguria from sulfathiazole treatment have been noted in a number of reports,^{11,41,52,59,64a,114} but ureteral catheterization and lavage have not been used in these cases.

Sulfadiazine has only been in use for a short time and it is probably too soon to evaluate the renal complications of therapy with this drug. Feinstone *et al.*³⁵ found almost no tissue damage from this drug in both monkeys and rabbits. In a summary of the renal complications in 872 cases collected from the early clinical reports,³⁶ hematuria²⁹ was found in 1%, anuria in one case, crystalluria in 11.7% and nitrogen retention in 1.1%. We have observed one case of anuria treated successfully by ureteral catheterization and another in which the procedure was applied late and proved ineffective. Dowling *et al.*³² have recently reported slight nitrogen retention (levels of blood urea nitrogen remaining below 50 mg. per 100 cc.) in 2 of 137 cases treated with this drug. They found crystalluria less often than with the sulfapyridine or sulfathiazole.

Sulfonamide Crystalluria. Several authors have described the crystals found in the urine of patients who are under treatment with various sulfonamide drugs. Stewart *et al.*¹¹⁶ identified the crystals in their cases as acetyl sulfanilamide but did not describe them. Antopol⁹ described "arrow-head" crystals in the urine of a sulfapyridine-treated patient. Plummer and McLellan noted similar forms.⁵⁵ Backhouse¹³ described the crystals of acetyl sulfapyridine and identified them. Sadusk presented illustrations of crystals from the urine in patients treated with sulfapyridine¹⁰³ and with sulfathiazole.¹⁰¹ The latter have also been illustrated by Sunderman and Pepper,¹²¹ who identified them as acetyl sulfathiazole.

Prien⁹⁹ suggested the use of polarized light to identify the various sulfonamide crystals found in the urine. He and Frondel⁹⁰ described the crystalline forms of the free and acetylated varieties of sulfanilamide, sulfapyridine and sulfathiazole. Their excellent and accurate description and photographs of the crystals as seen by the ordinary microscope should be a great aid in their identification.⁹⁰

Whether renal complications result more frequently in an acid urine than in an alkaline urine has been a subject of more speculation than objective study. Schwartz *et al.*¹⁰⁵ found that sulfathiazole crystalluria was less frequent if patients received equal doses of sodium bicarbonate with their drug. There is no agreement as to whether renal com-

Erobacter, *in vitro*, showed that the bactericidal and bacteriostatic effect of sulfanilamide in urine is closely related to the inoculum. A small number of organisms was often killed by low concentrations, while large numbers grew rapidly in high concentrations of the drug. More recently, Hill⁵⁰ showed that urine from patients receiving sulfathiazole by mouth has a greater bacteriostatic action than when this drug was added to urine in the same amounts *in vitro*. This would indicate that the drug may be changed and potentiated during its excretion into the urine. Helmholtz and Osterberg⁴⁹ also noticed the greater bactericidal power of the urine of sulfanilamide-treated patients as compared with the *in vitro* action of this drug. They found that acetyl sulfanilamide in concentrations up to 200 mg. per 100 cc. had no bacteriostatic effects against any of the common urinary pathogens at all pH levels tested.

Mellon and Shinn⁷⁴ showed that sulfanilamide has greater bacteriostatic power in urine than in broth and that urine lost its "potentiating" effect for *E. coli* when contaminated with broth. Spink¹¹³ showed that staphylococci are readily killed by sulfanilamide in urine, but are only slightly affected in broth. He recognized that even urine is not an optimum medium and noted that small quantities of broth destroyed the bactericidal power of the drug in urine. He also found that the bactericidal power of sulfanilamide in urine is greatly increased by raising the temperature. Several workers have attempted to correlate clinical with *in vitro* results. Vest *et al.*¹²⁷ found a good correlation between clinical cures and the *in vitro* effects of the drugs used on the patients' organisms. Others found no close correlation.^{75, 93, 94}

Chronic and Complicated Cases. Ballenger *et al.*¹⁴ pointed out that foci or "dead spaces" in the urinary tract may contribute to many of the failures of sulfonamide therapy. Most authors are agreed that cures are difficult to attain in cases of chronic urinary tract infections and in those in which there are important complicating factors. Mitchell *et al.*⁷⁶ cured 85% of their uncomplicated urinary tract infections, and only 30% of those that were complicated by strictures, stones, tumors or other lesions. Others have had similar experiences.^{7, 27, 33, 93, 94}

Relapses of infection in the urinary tract are not uncommon following sulfonamide therapy. Kenny *et al.*⁹⁶ noted an instance in which colon bacillus infection relapsed during the puerperium. Alyea and Roberts⁷ noted at least 7 relapses in over 200 patients. We have found that, in general, cases of chronic urinary tract infection may have temporary clearing of the bacilluria and of the abnormal urinary findings, but these frequently recur. In acute infections, relapses have been noted, in cases associated with apparently susceptible organisms, when the dose has been inadequate or the treatment discontinued too soon. Such cases usually respond when treatment is resumed with adequate doses for a long enough period.

Treatment of Acute Glomerular Nephritis. Williams *et al.*¹³³ used sulfanilamide in the treatment of about 50 patients with acute glomerular nephritis and followed their cases over a period of 2 to 3 years. They felt that the course of the acute disease was shortened. Eventually they had more cures in their treated patients than in a large number of control patients from whom sulfanilamide was withheld.

Dosage. The doses of the sulfonamides used to treat urinary infections have been lower, in general, than those used to treat other infec-

Proteus bacillus infections appear to be quite resistant to sulfanilamide^{34,48a,75} and so are those due to *Ærobacter ærogenes*.¹⁰⁹ *Pseudomonas* infections are completely resistant to sulfanilamide.^{48b,109}

Austen¹² used sulfanilamide-maltoside, a very soluble conjugate, in the treatment of urinary tract infections by pelvic lavage. He achieved bacteriologic cure in 1 of 10 cases and recommended this treatment for selected cases.

Albright *et al.*⁴ used sulfanilamide in the treatment of 2 patients with *Hæmophilus influenzae* pyelonephritis complicated by diffuse nephrocalcinosis and a persistently alkaline urine. The urines in both of these patients were eventually sterilized and became acid, thus removing what they believed to be an important factor in the etiology of the calcium deposition.

Sulfapyridine has not been used extensively in urinary tract infections. Melton⁷⁵ found that it was ineffective against *Strep. fæcalis* and gave a variable response in proteus infections. In colon bacillus and staphylococcal infections it was about as effective as sulfanilamide.

Sulfathiazole has already been used quite extensively in urinary tract infections. Helmholz^{48b} emphasized its effectiveness against the staphylococcus and found it superior to sulfanilamide against *Strep. fæcalis* but ineffective against *Pseudomonas æruginosa*.^{48b} Rammelkamp and Stoneburner⁹³ found sulfathiazole to be highly effective in acute uncomplicated cases of colon and *Proteus bacillus* infections and obtained marked improvement in other cases. Pool and Cook⁸⁶ cured 3 of 7 cases of *Strep. fæcalis* infections with sulfathiazole and sulfamethylthiazole. Culp²⁷ found sulfathiazole effective against *Staph. aureus* and *albus*, *B. proteus*, *E. coli*, *Ærobacter ærogenes*, *C. xerosis* (which he includes as a pathogen) and alpha streptococcus (*mitis*), but *Strep. fæcalis* proved resistant.

Rammelkamp and Stoneburner⁹³ found that sulfathiazole in a concentration of 10 mg. per 100 cc. in urine was more bacteriostatic than sulfanilamide, sulfapyridine or sulfamethylthiazole against staphylococcus and against colon, proteus and ærobacter organisms.

Sulfadiazine has not been used long enough to determine its exact place in the treatment of urinary tract infections. Feinstone *et al.*³⁵ found this organism highly effective *in vitro* and in experimental animals against *Staph. aureus* and Type B Friedländer bacillus. Long^{64b,c} also found it effective in mice against these organisms and against *E. coli*. Klinefelter⁵⁸ found it more effective than sulfathiazole against *E. coli*, both *in vitro* and in experimental infections in mice. Finland *et al.*³⁸ found it as effective as any other common sulfonamide drug in urinary tract infections. It was found to be particularly effective in acute colon bacillus infections.

In Vitro Studies. Several workers studied the effect of urinary pH on the *in vitro* action of the sulfonamides.^{48b,49,50,56,75,109,128} In general, they found them to be more bacteriostatic at higher pH levels for a variety of organisms. This is particularly marked in the case of the action of sulfathiazole on staphylococci. Melton⁷⁵ found sulfanilamide and sulfapyridine to be equally effective against *E. coli* at pH 6.7 and at pH 7.5. Kenny *et al.*⁵⁶ also found sulfanilamide to be effective against these organisms in a wide pH range.

Vest *et al.*,¹²⁷ working with staphylococcus, *E. coli*, *B. proteus* and

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tions. Alyea and Roberts⁷ found that doses of from 1.8 to 3 gm. daily were as effective as larger doses. Barr¹⁷ advises doses of 1.8 to 2.4 gm. of sulfanilamide daily. Mitchell *et al.*⁷⁶ started with very small doses which they increased daily until they obtained bacteriostatic levels of the drug in the urine, and then maintained these doses. Their maximum dose was usually about 4 gm. Both these groups of workers reported fewer reactions with the smaller doses. Helmholtz^{48b} emphasized the fact that very small doses of sulfathiazole are sufficient to inhibit the growth of staphylococci. Culp²⁷ used doses of 1.9 to 8.7 gm. daily, but in most of his cases he used 4 gm. daily (in divided doses).

Rammelkamp and Stoneburner⁹³ concluded from their *in vitro* and *in vivo* studies with sulfathiazole that concentrations of from 50 to 200 mg. per 100 cc. are usually sufficient to sterilize the urine and that such levels can be maintained by giving 2 to 4 gm. daily in divided doses. In cases of severe infections, especially those associated with obstruction, concentrations between 200 and 450 mg. per 100 cc. may be needed, and these require an intake of from 4 to 6 gm. daily. Gessler and Lippens⁴² found 2 to 3 gm. of sulfanilamide daily sufficient to cure colon bacillus infections. The early successes of Kenny *et al.*⁵⁶ are interesting in that they used 0.5 or 0.6 gm. of sulfanilamide three times a day in their cases. Bandstrup¹⁵ used similar doses in his cases with good results. Carroll *et al.*²¹ usually gave doses of 4 gm. daily, but they sometimes used 14 gm. a day when it seemed indicated.

Fluids. The effect of the volume of fluid intake upon the efficiency of sulfonamide therapy is a subject on which many have expressed opinions but few have presented convincing data to support them. The admonition to restrict fluid intake during sulfanilamide administration has been widely enunciated and practised. The studies of Alyea *et al.*⁷ have shown that the size of the dose of sulfanilamide and the volume of the fluid intake made little or no difference in their clinical results. With sulfapyridine and sulfathiazole, the necessity of maintaining a large urinary output in order to prevent urinary complications precludes the restriction of fluids.

Complications of drug therapy in urinary tract infections are the same as in the treatment of other infections. As already mentioned, they may be less frequent if smaller doses are used. Carroll *et al.*²¹ found complications requiring the cessation of drug therapy in 15% of sulfathiazole-treated patients. Culp²⁷ observed a large number of complications in sulfathiazole-treated patients and stated that most of them occurred in the presence of high blood levels. The almost complete absence of complications in the cases reported by Gessler and Lippens⁴² and by Kenny *et al.*⁵⁶ are interesting since they used very small doses of sulfanilamide. In patients with good kidney function, there seems to be no positive evidence that renal complications of sulfonamide therapy are more frequent in the treatment of urinary tract infections than in the treatment of other infections, such as pneumonia.

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RADIOLOGY.

UNDER THE CHARGE OF

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PULMONARY TUBERCULOSIS.

ROENTGENOLOGISTS, as a result of experience, have well-formed concepts of the roentgenologic appearance of pulmonary tuberculosis in its varying types and combinations of types. These concepts include characteristics of the shadows and typical locations of the lesions, and are so accurate that the wise pathologist at necropsy will use all the resources at his command before he disputes the diagnosis of the roentgenologist. With this introduction, Birkelo, a roentgenologist, and Brosius,² a pathologist, presented a series of cases, in each of which a diagnosis of pulmonary tuberculosis had been made from the roentgenographic image and correlation of the data of the clinical history and physical examination. In all of these cases, the major illness subsequently was proved to be non-tuberculous. The cardinal symptoms of pulmonary tuberculosis, cough, hemoptysis, thoracic pain, loss of weight, night sweats, and fever were present in varying combinations and in varying degrees in all of the cases.

These cardinal symptoms, Birkelo and Brosius² asserted, are common to so many pulmonary diseases that they are not, in themselves, diagnostic. They pointed out that cough, when productive of foul sputum, indicates pulmonary abscess or bronchiectasis, but can be a feature of tuberculosis in which there is excavation and secondary infection. Hemoptysis, although it frequently occurs in tuberculosis, also can occur from pulmonary congestion resulting from cardiac lesions or from ulcerating lesions of the bronchial tree, the latter including cancer and bronchiectasis. In their experience, thoracic pain is usually less prominent in tuberculosis than in cancer and pneumonia. Although loss of weight is nearly always present in cancer and usually is a feature of tuberculosis, it does occur in other debilitating and chronic pulmonary diseases. Even the history of exposure to tuberculosis, or the eliciting of roentgenographic evidence of previous tuberculous infection, they found, can be either misleading or helpful and has to be evaluated with extreme caution. Night sweats and fever, in their experience, are the least diagnostic of the so-called cardinal symptoms. They regarded sudden onset of a tuberculous infection as much more common

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Ghon as having asserted that about 85% of cases were of this type. In Sweany's experience these lesions resulted from a single area of infiltration that had definite central caseation; this was first apparent in the roentgenogram as a cloudy infiltrate, with poorly defined borders, which gradually cleared from the nebulous mass to a more discrete shadow with a sharper border. The decrease in size of the primary lesion he found to be rather rapid during the first year; later the decrease in the diameter was approximately 10% per annum for several years. The contraction apparently resulted from the laying down of new fibrous tissue each year during the first 6 to 8 years. Further disintegration continued from within by a process of resorption.

The first evidence of primary tuberculous lesions in childhood is distinguishable from pneumonia by correlation of the roentgenographic features with the clinical data. Onset of the primary tuberculous lesion is insidious or attended with little more than an ephemeral initial fever which is frequently considered as "grippe." This fever rarely lasts more than a week or 10 days and may last for only a few days. In the majority of cases tuberculosis is asymptomatic within 2 weeks after its appearance of the allergic phase. When marked symptoms do appear, the possibility of beginning ulceration or mixed infection must not be overlooked. The changes in the degree of contraction and the over-all density of the various lesions observed were consistent and indicated clearly that the age of these could be estimated roughly by observing roentgenographic densities on serial roentgenograms made over a period of 6 to 8 years after infection.

In a fourth group of cases the author placed those in which large infiltrates had been resorbed and had left behind various "shrapnel-like" areas of calcification. He found that a large focus may clear and leave a large number of calcified foci that produce a roentgenographic image similar to that of the calcification in a healing re-infection type of lesion. Generally, a whole lobe was involved in the infiltrative process; occasionally infiltrates had cleared around the border and left circumscribed, poorly calcified masses. In some cases the circumscribed masses had broken up into smaller foci as a result of the penetration of the central mass by capillaries and subsequent proliferation of reticulum and fibrous tissue. The basic reticulum in these masses apparently persisted for long intervals after encapsulation and was revived by the inroad of new capillaries.

A fifth group was comprised of cases in which ulceration or overflowing of the lesion led to an exacerbation of the disease. The impression gained was that a single focus may ulcerate after calcification and present the paradoxical roentgenographic image of a focus that had the appearance of healing, yet was in reality an open lesion communicating with a bronchus. A small primary focus could ulcerate to set up disease. Sweany averred that if only 1 lesion out of a 100 should ulcerate in this manner much of the adult type of pulmonary tuberculosis could be explained. In his experience when these lesions do ulcerate, most of them open up early and remain open for a few weeks to many years before causing clinically significant disease. It was conceivable, he thought, that some lesions might not ulcerate until years after calcification. At other times the infiltration might become resolved into calcified foci numbering into the hundreds and involving an area ranging

than was realized before Roentgen rays were available. They also learned that non-tuberculous pneumonic consolidations can persist long after the subsidence of acute symptoms.

Included in the list of pulmonary diseases which simulated tuberculosis sufficiently to have resulted in diagnostic errors were bronchopneumonia, pulmonary abscess, bronchiectasis, pulmonary cystic disease, primary cancer of the lungs, metastatic cancer, silicosis, pulmonary moniliasis, actinomycosis, blastomycosis and syphilis of the lung. Cardiac disease and chronic valvular heart diseases, they found, produce infiltrates or pulmonary fibrosis which simulate closely those characteristic of some types of pulmonary tuberculosis. The significant roentgenographic image in each case that had suggested the erroneous diagnosis was described and discussed from the standpoint of differential diagnosis. The information gained by this dual effort of a roentgenologist and a pathologist, as it was expressed by them, might well be accepted by all interested in the subject of pulmonary tuberculosis as a creed: "Our mistakes, appreciated and corrected, teach us more than our successes, and each difficult case, finally solved, leads to a better understanding of other diagnostic problems. The more we can share our experiences, the better will be our mutual understanding, the more tolerant we become of the mistakes of others, and the more efficient we become as individuals."

Sweany⁸ in a presentation of his work on the primary tubercle declared that the best means of obtaining information with regard to the progressive ageing of primary tubercles that would be useful for the living seems to rest in the field of roentgenology. He felt that to know better the significance of roentgenologic shadows and to facilitate an understanding of them, it is expedient first to interpret them in terms of pathology through the medium of the postmortem roentgenogram and postmortem examination. This knowledge, he asserted, could then be used in order to understand better the shadows cast on antemortem roentgenograms and to translate the findings into terms of morbid anatomy, the foundation of all medicine. With the aid of 38 excellent roentgenograms, this author comprehensively covered the various manifestations of pulmonary tuberculosis in childhood. The types of lesion were arranged as much as possible with respect to their evolution, as revealed on roentgenograms, controlled by previous pathologic observations.

The lesions in Sweany's first group included small foci communicating with the bronchi, which were frequently not visible on the roentgenogram until the disease was well advanced, and also those in which massive involvement had occurred which presented the roentgenographic picture of ulcerative phthisis throughout. The second group consisted of an ephemeral type of lesion that usually left no calcified tissue at all, at least none that could be observed on the antemortem roentgenogram. In some of these cases only the lymph nodes were involved; in a few small calcified foci were exhibited for 10 or more years. This type, in Sweany's opinion, probably accounted for a large percentage of "tuberculin-positive, roentgen-ray-negative" cases, especially after deduction of about 15% for cases of extrapulmonary infection. Lesions of the third group were the most common; the lesions of this group left only one calcified focus in the parenchyma. Sweany quoted

considered tuberculosis to be the causative factor a considerable accentuation of the shadow of the hilar lymph nodes bilaterally.

Mayoral,⁵ in a discussion of this type of lesion, was convinced by Sayers and Meriwether's evidence that these lesions were of mycotic origin; they stated that *Aspergillus niger* was the etiologic factor. Mayoral credited Virchow with calling attention to similar calcium deposits in the lung as early as 1855. Virchow had noted these in the lungs of patients suffering from extreme caries or some other destructive condition of bone and named these deposits "calcium metastases." Mayoral felt that the clinical conception of miliary tuberculosis as a rapidly fatal disease was not sustainable in the face of roentgenographic evidence of miliary "seeding" in cases in which the patients had apparently outlived an infection of miliary type. In addition, other patients were encountered who, from all appearances, were in perfect health and yet the roentgenograms revealed shotlike intrapulmonary areas of calcification not unlike those of the miliary type of tuberculosis in distribution. Mayoral mentioned personal observations of mine concerning this lesion reported in 1925. When the individual calcified areas are thoroughly discrete, I am inclined to the belief that these are phleboliths or have some other etiologic factor than tuberculosis. Calcifications resulting from tuberculosis are, in my experience, invariably irregular or ragged in their outline. They appear in the roentgenograms as small areas of ossification in tissues that have undergone changes akin to those produced by ulceration from other causes. Mayoral stated that no satisfactory criterion has been offered for differential diagnosis. Experience has been that lesions of this type are generally clinically insignificant and, because of this, have rarely become the subject of postmortem examination.

In his study of tuberculous lesions confined to the lymph nodes, Sweany concluded that the capsule of the lymph node offered a barrier that was comparable to the pleural layer around the parenchyma of the lungs. He averred that there is a constant diffusion of toxins through the capsule into the surrounding tissues. He considered this phenomenon responsible for many pathologic changes in the perivascular tissues around the bronchi which produce many clinical effects. This fact, in his opinion, was not sufficiently well appreciated by those interested largely in tuberculosis. The lymph nodes of children, he found, were more prone to be involved than those of adults. The lesions occurred in a single focus or several foci. Caseation sometimes involved the whole node, which underwent hyperplasia. The majority of these lesions did not result in changes which made them demonstrable on the antemortem roentgenogram. In some cases varying degrees of thickening of the hilar shadow were apparent in the roentgenogram. He found that lesions of the lymph nodes showed resorption, especially those in which simple inflammation or early calcification occurred, but those in which definite calcification was present seemed to resist resorption to a greater degree than lesions in the parenchyma of the lungs. Just as was observed in the parenchymal lesions, the majority of lesions of the lymph node healed. Certain ones remained open, however, to overflow and cause a spread of the disease by blood, by lymph or by bronchial routes. By this spread the lesion within the lymph node, in some cases, assumed an almost malignant character. He noted excavation of the lymph nodes, into the bronchus most commonly but

in extent from a part of a lobe to a whole lung. Such lesions frequently presented the "shrapnel-like" roentgenographic image heretofore mentioned. Many of these lesions healed completely, but occasionally dormant foci became active years afterward and caused cavity formation.

When the defensive action of the lung was impaired, as in silicosis, and on rare occasions in uncomplicated tuberculosis, this overflowing progressive or flowing type of lesion and its characteristic roentgenographic image might be encountered. Sometimes only one or two such lesions appeared to progress, while the others healed. Sweany considered that an important factor might be focal accumulations of bacilli. While some lesions spread rapidly, others seemed to progress slowly; some spread in the parenchyma while others progressed in the lymph nodes; some were observed to spread at different rates of speed in different parts of the same lung. The evidence seemed to be sufficient, in his opinion, to warrant caution in the use of the term "healed Ghon focus" to describe any of these lesions.

The clinical significance of the primary tubercle was summed up by Sweany as follows: The majority of lesions do not spread at all; that is, they heal. A relatively small number progresses, but because so many of these come to the attention of physicians, they seem to be relatively more numerous than they actually are. A common type is the one in which several foci progress simultaneously, as in silicosis and in non-immune races of people. Occasionally only one tubercle of the primary complex progresses and becomes obliterated; the remainder of the tubercles are left as healed "Ghon foci" and there is no evidence of the cause of spread of the disease. The reason for these progressive lesions is still one of the unsolved problems of tuberculosis. Such tubercles might appear to be recent fibrocaseous formations, yet they may have been enlarging over a period of years; it was possible to observe this in a study of serial roentgenograms. The capsule was apparently inadequate to hold the organisms within the center of the focus. The reason for the breakdown of the defense mechanism varied; this might be due to partial exhaustion of the defense mechanism which allowed continual escape of the organisms through the thin-walled capsule. It might be due to an increase in virulence of a particular colony of bacilli. A factor in the creation of the roentgenographic image of some of the lesions might be the spread of toxins causing a stimulation of new fibrous tissue outside the capsule; as the spread continues into neighboring alveoli and bronchioles, these structures become obliterated and enmeshed in fibrosis. A few organisms might follow down the bronchioles or lymph tracts; some might get into the capillaries and travel to other parts of the lung or of the body. Because of the comparatively small number of these organisms, most of them are destroyed. Not until the tubercle encroaches on a larger bronchus or blood-vessel is there real danger of sufficient spread to cause clinically significant disease.

Sweany placed in a sixth group lesions which he considered were concerned with the hematogenous spread of bacilli through the lymphatics or blood stream after primary infection. The roentgenographic picture in this group was that of miliary calcification widely distributed throughout both pulmonary fields. He noted in cases in which he

of making spot roentgenograms to afford a permanent, and at the same time, a more explicit record of the image seen on the fluoroscopic screen. In a series of 37 illustrations made from spot roentgenograms he clearly demonstrated small infiltrates that were easily capable of being obscured and missed in the roentgenogram. Stiehm expressed the opinion that the skepticism existing regarding the efficacy of roentgenoscopy in the visualization of small parenchymal lesions was unwarranted. Roentgenoscopic examination, made by a trained and experienced observer, he considered, was more efficient in finding minimal lesions, particularly those involving the parenchyma, than roentgenographic examination, with the use of a single roentgenogram or roentgenograms made in stereoscopic sets.

In 87% of the cases, pulmonary tuberculosis is not discovered until it has passed beyond the minimal stage. Such statements as this, published by Badger and Ritvo¹ in the discussion of the value of the tuberculin test and the roentgenogram in eliciting evidence of early tuberculous lesions, have greatly stimulated thought and effort in the search for methods of making the diagnosis of pulmonary tuberculosis in the earliest possible stage. They compared the data from a survey commenced in 1932, for which all nurses admitted to training were given a tuberculin test, roentgenographic examination of the thorax and a complete physical examination with the data of Heimbeck, who thought that a positive reaction to tuberculin before admission was indicative of conferred immunity. Badger and Ritvo felt that no sweeping conclusions were justified concerning the vulnerability of those who had initially negative reactions to tuberculin as compared with those who initially had positive reactions. The tuberculin test, they averred, should be used as a means of detecting the presence of tuberculous infection. A negative result from a tuberculin test on strong healthy young persons indicated the absence of tuberculous infection. But the result of the tuberculin test could not be considered negative unless the individual had failed to respond to 1 mg. of old tuberculin or its equivalent. A positive tuberculin reaction proved the presence of infection somewhere in the body; it did not afford any information concerning the anatomic site or extent of the lesion or of its degree of activity or non-activity in any given case. An initially negative reaction that later becomes positive indicated the appearance of a so-called primary or first infection form of tuberculosis. In the experience of these authors, all of those nurses who had negative reactions to tuberculin at the beginning of training later had positive reactions, but a tuberculous infection with changes that made the lesion roentgenographically demonstrable developed in only a few instances. It was concluded that the primary infection of some adults may be as benign a process as that of children usually is. The usual benign primary infection developed in a region or state not demonstrable by Roentgen examination in the majority of both groups studied by Badger and Ritvo. A few patients presented roentgenographic evidence of lesions without clinical manifestations of disease. Others progressed to clinically active tuberculosis. The small roentgenographically demonstrable lesion might be the single positive finding when an exhaustive study of the individual case was completed. Repeated roentgenographic studies, weekly and later monthly, were necessary under these circumstances to determine, if possible, whether the lesion was an old healed scar, a latent process which might break down at some future time, an

occasionally into the mediastinum, the esophagus or the trachea in one particular group of cases. In another group he regarded the changes demonstrable in the roentgenogram attributable to swelling of lymph nodes and also to the perifocal toxic effect of the tubercle bacilli. Stagnation of blood and lymph occurred which resulted in effusions in the tissues or in the pleural cavity; this, he thought, was suggestive of an interference with normal function. Evidence of catarrhal bronchitis was noted; an increased flow of mucus resulted which together with the external pressure of the lymph nodes, lead to atelectasis. Late effects, attributable to contraction of fibrous tissue and leading to constriction, could, Sweany thought, have a part in the creation of the characteristic roentgenographic image.

Sweany offered a most significant explanation for the more or less widespread ignorance of the roentgenographic images of the primary tubercle, and the fundamental importance of a knowledge of these to a clear understanding of pulmonary tuberculosis. He stated that practically all significant lesions are apparent in roentgenograms when they are in the infiltrative stage, but relatively few roentgenograms are made of primary lesions in this stage, because in the majority of cases the infiltrates occur without producing symptoms. These infiltrative lesions are demonstrable roentgenographically for only 6 months to a year, after which they shrink into "Ghon foci," frequently become non-demonstrable or gradually disintegrate and disappear. He considered the statement, that much less than a third of significant primary tuberculous lesions were demonstrable on routine roentgenograms taken in the anteroposterior position, to be conservative. Improvement in roentgenographic technique, especially by varying the quantity of Roentgen rays and taking more serial roentgenograms, he thought, would greatly enlarge the scope of observation.

The work of Fellows and Ordway, Reid and Hetherington, and Flahiff demonstrated that roentgenoscopic examination of the thorax was far superior to physical examination in finding tuberculous lesions. Reviewing the reports of these observers, Stiehm⁷ quoted Fellows and Ordway as having found that 87% of the lesions discovered by roentgenographic examination were visible in roentgenoscopic examination. In the experience of Stiehm, neither method revealed all the existing lesions or abnormalities. In the course of 5 years, during which he employed roentgenoscopic examination as a daily routine and compared the results with those attained from single roentgenograms or roentgenograms made in stereoscopic sets, he became convinced that certain lesions involving the lungs, particularly those in the extreme apexes and supraclavicular areas, did not show at all or at least not to the same advantage in the roentgenogram as they did on roentgenoscopic observation. To compare the results of roentgenoscopy with those of roentgenography better, Stiehm used both methods to examine 423 consecutive patients. A single roentgenogram was made in the postero-anterior position and the results of the dual examinations were charted. The charting revealed negative roentgenographic and roentgenoscopic reports in 293 cases. Comparison showed no error made by either method. On roentgenographic examination, 385 (91%) of existing lesions were detected and 38 (9%) were missed. In roentgenoscopic examination, 405 (96%) of existing lesions were reported and 18 (4%) were missed. Convinced by these experiences, Stiehm devised a method

The most practical application of all the principles involved in this survey method of eliminating tuberculosis was reported by Sheldon.⁶ Every applicant accepted for enlistment in the United States Navy was sent to a naval training station and kept in detention there for a period of 3 weeks, in order to permit the development of any common communicable disease resulting from any exposure. In that interim it was possible to make an examination of the thorax with the aid of Roentgen rays. Photography of the image on the fluorescent screen (fluorography) on 35 mm. film in rolls was employed. All persons found by this method to have positive or suspicious evidence of incapacitating disease were sent to naval hospitals for observation and further study. When a diagnosis of pulmonary tuberculosis was established and confirmed, the afflicted persons were discharged from the service because of disease that existed prior to enlistment. By this procedure claims on the Government for pensions were eliminated. When these patients were discharged, local or state authorities concerned were notified of this action, in the hope that steps would be taken to place the discharged persons under adequate treatment and thus the interests of the individual and, at the same time, those of the community would be protected. These authorities were requested to report the condition of the patient to the naval medical officers at the end of 6 months. By this arrangement, the diagnosis was again confirmed and an opportunity was afforded to check for possible errors in diagnosis.

The appearance of this interesting series of publications in journals of recent date proves that the members of the medical profession are alert to the needs of the national preparedness program and are prepared to meet the problems involved with methods that are efficient, practical, and at the same time helpful in conserving the resources of the nation.

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early destructive lesion, or a benign and innocent process which would heal spontaneously. Constitutional resistance, in their experience, was a feature of the disease which could not be predicted, but it was most important in prognosis and in the development of immunity in cases of infection by the tubercle bacillus.

In an anatomic roentgenographic study of the pleural domes and the pulmonary apexes, Jamison⁴ found that subpleural apical scars were of non-tuberculous origin in many, if not the majority of such lesions. He found that the incidence of these lesions increased in frequency with advancing age. He demonstrated that normal structures could cast shadows on the roentgenogram that could easily be erroneously interpreted as those of definite lesions.

In a discussion of the relation of public health to the preparedness program, Wirth⁹ quoted remarks of Parran concerning the problems associated with the coordination of research and the development of practical methods of prevention of certain communicable and infectious diseases which are major hazards to successful defense. Among the problems was the handling of cases of tuberculosis discovered by the medical consultants associated with the draft boards. Wirth stressed the grave responsibility which rested on the roentgenologist of each community in the service of the local draft board in the detection and weeding out of persons suffering from tuberculous infection. He pointed out the fallacy of allowing the victims to be sent back to work in industry and to spread pulmonary tuberculosis among their families and their associates. He deprecated the fact that only 15% of the industrial workers in the United States were employed in industries which provided organized facilities for the maintenance and promotion of the health and hygiene of employees. He inferred at least that it was inimical to the interests of the remaining 85% that they had to rely on general practitioners to protect their health and to care for their injuries. He felt the solution of the problem involved territorial, local and state health officials, as well as individual physicians, medical organizations, philanthropic organizations, industrial and labor organizations, and even private individuals. The fear of many, he stated, was that the greater the emergency, the greater would become the centralization. The extent to which this would occur, in his opinion, would be determined by the degree of concern of each person with our present way of life and the diligence and spirit of public service with which each person performed each task as it arose.

The report³ of a committee to the Board of Chancellors of the American College of Radiology revealed that attention of the roentgenologists has already been focused on this problem. The committee found that surveys on tuberculosis have been widely used by local and state boards of health, by local and state tuberculosis associations, under the auspices of boards of education, industrial insurance carriers, large-scale employers and other official and quasi-official bodies. The chief function of any survey, the committee felt, should be the elimination of the healthy from consideration so that those who need roentgenographic examination of the thorax may be identified. The value of a survey depends on two factors: 1, the technical quality of the roentgenographic image attained by any method; and 2, the training and experience of the person or persons interpreting the characteristics of this roentgenographic image.

The following hematologic examinations were made as soon as possible after the removal of the blood:

Red blood cells were counted in the usual manner with Thoma micropipette and Neubauer counting chamber. Hemoglobin was determined by the oxyhemoglobin method in a Klett-Summerson photoelectric colorimeter using 0.025 cc. of whole blood in 5 cc. of distilled water. The reading was made following centrifugalization of the mixture for 30 minutes in order to settle the gross parts of stroma.

Packed red cell values were obtained using the Wintrobe hematocrit tube, centrifugated at 3000 rotations per minute for 30 minutes.

Reticulocyte counts and counts of red blood cells with Heinz corpuscles were made as described below. Brilliant cresyl blue (0.2 gm.) was pulverized in a mortar and dissolved in 100 cc. of 0.6% sodium chloride solution. This gives a final solution of practically the same tonicity as blood plasma, a point of paramount importance in this method. This solution must be filtered twice and kept in very well closed bottle to avoid evaporation and consequent changes in tonicity. One drop of this solution is mixed with 1 drop of blood and observed as a wet preparation between slide and coverslip. Sealing with vaseline is not necessary as the counts must be made within 10 to 15 minutes, during which time the amount of evaporation is negligible. The red blood cells should be allowed to settle to the bottom of the preparation before making the examination. Care must be taken not to prepare thick preparations, since erythrocytes must be isolated to permit careful examination. This can be achieved with practice by using proper amounts of cresyl blue solution and blood when preparing the slide.

The reticulum of reticulocytes appears deeply stained blue against the green color of the protoplasm. Usually, one also observes metachromatic granules stained light red. Heinz corpuscles do not take the stain and appear as highly refractile crystal-like bodies green in color but of greater intensity than that observed in the erythrocyte protoplasm. Heinz granules show very marked Brownian movement when small and appear in any part of the red cell but are usually in the periphery, frequently they protrude from the side of the cell. When large doses of pyridin are employed to produce anemia, several granules may be seen in the same cell, but with medium or small doses only one granule is seen. These granules are very small after the first injection but grow progressively larger until they attain almost one-fifth of the red blood cell mean corpuscular volume. The granules have a tendency to leave the cell and if the examination is not made as soon as the cells have been sedimented, many granules may be found free in the plasma.

To demonstrate more clearly that the reticulocytes are not attacked by pyridin a simple blood examination without any staining may be done. Heinz corpuscles appear as described before and the reticulocytes appear as normal untagged erythrocytes, sometimes with a very hyaline granule (metachromatic granule when stained by brilliant cresyl blue) like a white spot within the greenish protoplasm.

Resistance to hypotonic salt solution was determined by mixing 0.025 cc. of blood with 5 cc. of 0.5% solution sodium chloride in distilled water. After standing 3 to 5 minutes the non-hemolyzed red blood cells were centrifugalized and the amount of hemoglobin in the supernatant fluid determined in the Klett-Summerson photoelectric colorimeter. The result was compared with the hemoglobin reading of a tube containing 0.025 cc. of whole blood hemolyzed in 5 cc. of distilled water, hemolysis representing 100%. Because the variation in resistance was very great in these experiments, this method was used in preference to the usual complete hemolysis curves determination.

Estimation of opacity of blood in distilled water was used as a measure of the total volume of Heinz corpuscles formed following pyridin intoxication.

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ORIGINAL ARTICLES.

ACETYLPHENYLHYDRAZINE ANEMIA. 1. THE MECHANISM
OF ERYTHROCYTE DESTRUCTION AND REGENERATION.

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THIS paper deals with preliminary studies of erythrocyte regeneration in acetylphenylhydrazine anemia—a condition in which many products of red blood cell disintegration remain within the body economy. Detailed hematologic observations of red blood cells made at short intervals of time and pathologic examination of tissues selected at critical points have proved useful in improving the understanding of physiologic agencies active in the destruction of damaged erythrocytes and in the reconstruction of new red blood cells. The observations described may to some extent be helpful in understanding types of anemia in which the organism does not need exogenous material to rebuild the destroyed erythrocytes.

Methods. Different types of dogs have been used in these experiments. Normal dogs (Nos. 39-1, 39-57 and 40-213); splenectomized dogs (Nos. 39-194, 40-115 and 40-152); dogs with a gall-bladder renal fistula (Nos. 37-137 and 40-248); dogs made anemic by bleeding, and therefore with depleted iron reserves (Nos. 39-26 and 39-299); as well as a dog with a Pavlov pouch (No. 39-317). Normal rabbits (Nos. 3 and 4) were also observed.

In all of these 13 animals acetylphenylhydrazine (pyrodin*) was used for red blood cell breakdown. The injections were made subcutaneously beneath the skin of the abdomen. Pyrodin was dissolved in 10 to 20 cc. of hot saline just prior to the administration.

Hematologic methods used required only small amounts of blood. Generally 1 or 2 cc., rarely 5 cc., were taken from the jugular vein for each sample. A dried mixture of potassium and ammonium oxalate (3 gm. ammonium oxalate and 2 gm. potassium oxalate in 100 cc. distilled water) was used as anticoagulant, 0.04 cc. of the solution for each cubic centimeter of blood.

* Eastman Kodak Company.

tion. Since these corpuscles do not dissolve, a turbidity developed when the blood from poisoned animals was diluted in water. After 30 minutes of centrifugalization all the corpuscles had settled to the bottom of the tube, leaving a clear supernatant fluid containing hemoglobin. If the extinction of light before and after centrifugalization is determined in the photoelectric colorimeter (really nephelometry in this case), the difference represents the amount of light absorbed by the Heinz corpuscles, the stroma absorption being negligible.

Experimental Observations. 1. *Formation of Heinz Corpuscles in the Erythrocytes.* In all of 20 breakdown episodes in 13 animals, 20 to 24 hours after pyrocin injections (14 mg. per kilo body weight in rabbits and 19 mg. per kilo in dogs) the presence of Heinz corpuscles was observed in *all* adult red blood cells in the circulation. Furthermore, the young red blood cells (reticulocytes) *never* demonstrated such a structure, even with repeated injections totalling large amounts of the drug (144 mg. per kilo). In one instance (Dog 39-317) when pyrocin (0.9 gm.) was injected at a very low anemia level, the presence of Heinz corpuscles was observed within reticulocytes containing very little amount of reticular substance, *i. e.*, in reticulocytes almost reaching the stage of young adult erythrocytes. However, even in this particular instance, the tagging of a young reticulocyte containing ample reticular substance with a Heinz corpuscle was never observed.

We have seen the formation of Heinz corpuscles *in vitro* with the technique described by Bratley and associates.⁶ The appearance of minute corpuscles, 5 or more in each erythrocyte, is easily seen after 10 to 20 minutes. *In vivo*, however, with small and medium doses, a single corpuscle is observed in each red blood cell; this corpuscle increases in size with the severity of intoxication. With massive doses we have observed, as *in vitro*, the formation of 5 or more corpuscles in each red cell. In fixed and stained smears the Heinz corpuscle is invisible when small, but if large enough, it may be seen as a mass staining red (1 to 2 micra in diameter), containing a very minute basophilic dot in the center. This is better shown when the blood is treated with distilled water, staining free corpuscles. Within the red cells the acidophilic structure of the Heinz body fuses with the red color of hemoglobin and then only its central basophilic granule (0.5 to 1.5 micra in diameter) can be seen. In red cell shadows following hemolysis in distilled water, the Heinz body remains within the limits of the cell border. These bodies have a circular shape, they probably are spheres because when a red cell is seen in profile the corpuscle is still circular in shape. As we have pointed out before, the size of the corpuscles increases with the severity of intoxication, therefore the measurement of their volume varies accordingly. We have tried to determine the volume of large Heinz bodies by observing the total volume of packed Heinz bodies from a known amount of hemolyzed blood. Their volume is roughly one-fifth that of the normal red

and is more rapid with small doses (daily output of 0.472 R.B.C. million per c.mm.) than with large (daily output of 0.290 R.B.C. million per c.mm.). The first period of regeneration is characterized by a steady increase in the number of the red blood cells. In the following period the rate of production is slowed down and continues until a normal level is reached. The end of the first period is attained in dogs in 10 to 11 days with small doses, in 16 days with large.

In rabbits, the disappearance of the erythrocytes containing Heinz bodies is much more rapid (8 to 9 days), the lowest anemia level is even lower than that in dogs, and is observed earlier (6 days after

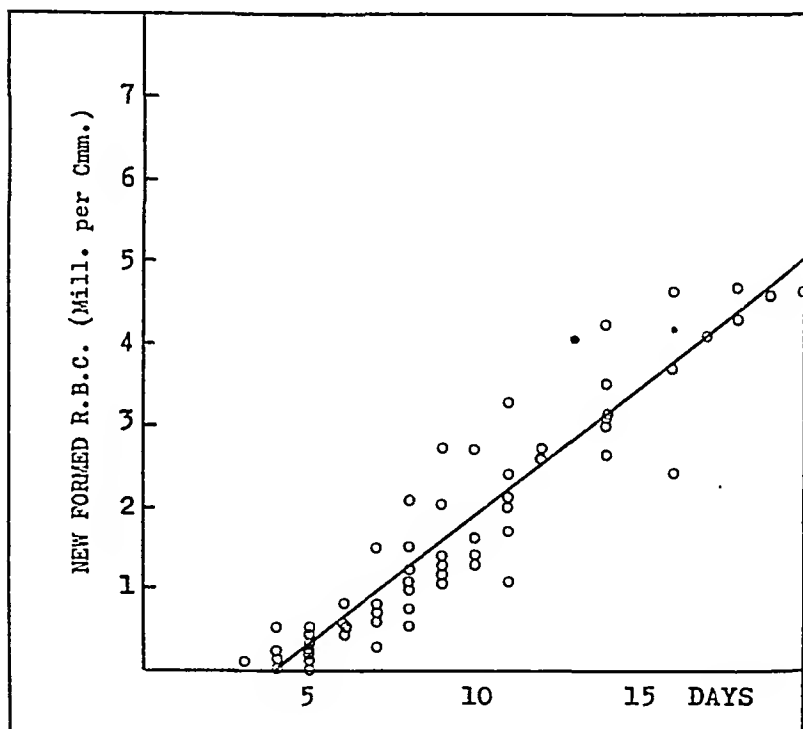


CHART 2.—The appearance of new formed red cells following pyridin anemia.

the first injection). Regeneration begins sooner (2 days after the first injection) but is almost at the same rate as that observed in the second group of dogs.

Chart 1 presents the disappearance of the red blood cells with the Heinz bodies from the blood stream of 8 dogs. Numerical decrease of these cells in the circulation is proportional to the time elapsed, as shown by the straight line. Chart 2 illustrates the appearance of newly formed cells in the blood stream of 8 dogs. It shows that regeneration (to subnormal levels values of 4 to 5 million R.B.C. per c.mm.) is proportional to time. To illustrate the picture during

cell. After hemolysis and centrifugalization, the Heinz corpuscle appears as a lightly colored mass, strongly bound together in the bottom of the tube. After long centrifugalization it is very difficult to get them again in suspension, so firmly are they coherent.

2. *Measure of Destruction and New Formation of Red Blood Cells.* Findings observed during destruction and regeneration of red blood cells are summarized in Table 1. Varying total amounts of pyrodim were employed in dogs for each breakdown episode ranging from 27 to 187 mg. per kilo body weight. As concerns the results, the

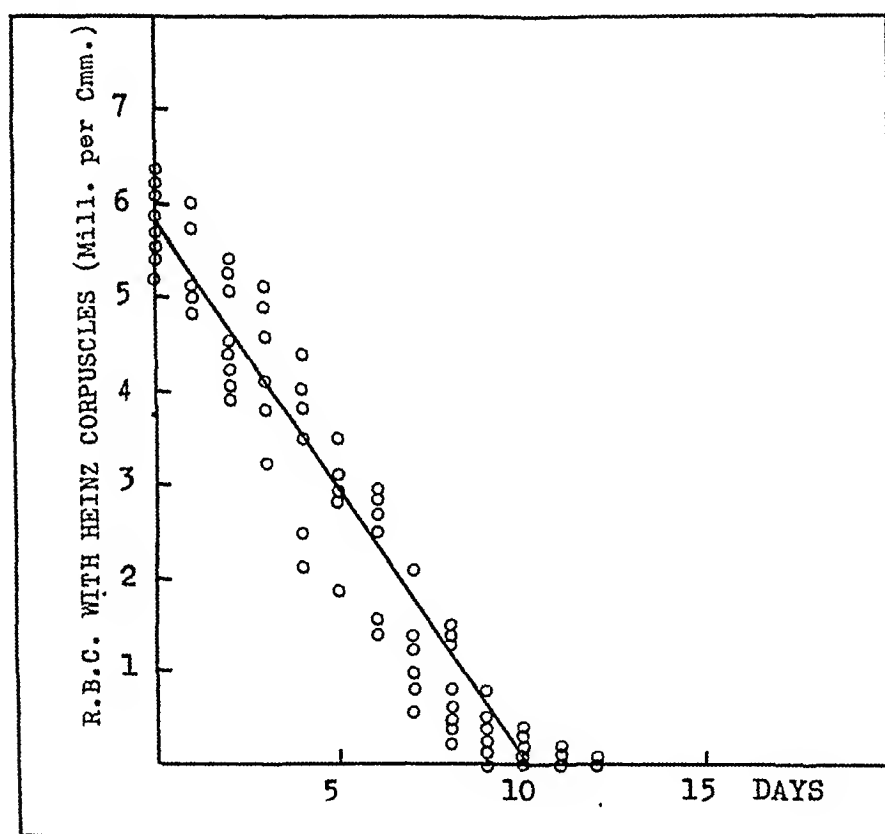


CHART 1.—The disappearance from the blood stream of erythrocytes containing Heinz corpuscles.

doses can be regarded as: small (27 to 40 mg.) and large (above 40 mg.). In small doses the rate of daily average disappearance is 0.416 million R.B.C. per c.mm., taking 12 to 18 days for complete disappearance. In large doses the rate of daily average disappearance is 0.490 million R.B.C. per c.mm., taking 9 to 14 days for complete disappearance.

The lowest anemia level in the first group (small doses) was twice as low as that in the second group (large doses). In both groups, it was attained 7 to 10 days after the first injection of pyrodim.

Regeneration starts 3 to 4 days after the beginning of intoxication

degree of red blood cells intoxication during the breakdown period, as measured by the total volume of Heinz corpuscles in circulation. It represents the results of 15 breakdown episodes in 10 dogs. As in Chart 3, illustrating fragility, the result shows a maximum intoxication on the fifth day after the first injection and complete disappearance of the corpuscles on the eleventh day. The first half of the curve shows a progressive increase in the volume of corpuscles as indicated by the increase in the opacity of the fluid when blood was mixed with distilled water. From the fifth day on opacity progressively decreased coinciding with the disappearance of the red blood cells with the Heinz bodies from the blood stream.

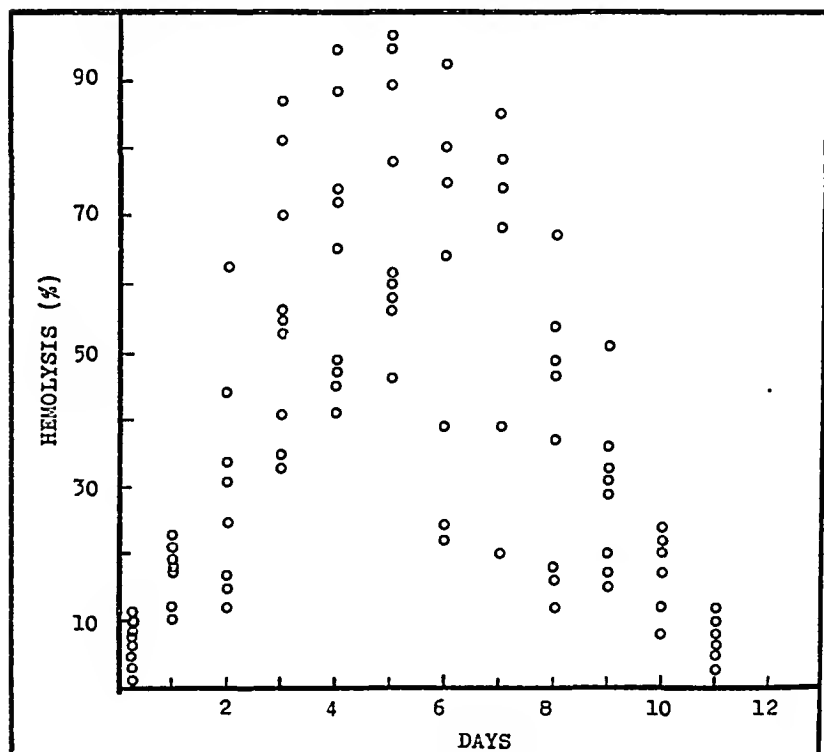


CHART 3.—Behavior of poisoned erythrocytes toward 0.5% saline solution.

5. *Higher Peaks of Reticulocytosis Observed During Regeneration.* Table 3 shows the peak concentration of reticulocytes in the regenerative periods. The number of reticulocytes in the peripheral blood seems to be proportional to the total amount of pyrodin given, or perhaps to the time in which this total amount has been administered.

Dog 40-115 could not be followed after the figures presented in Table 3 were reached. We believe, however, that the figure shown

the destructive phase and the subsequent regenerative phase, complete figures in 1 dog (No. 40-213) are presented in Table 2.

TABLE 2.—DETAILED HEMATOLOGIC OBSERVATIONS DURING DESTRUCTIVE AND REGENERATIVE PHASES OF PYRODIN ANEMIA IN A TYPICAL EXPERIMENT. (DOG 40-213.)

Days of observation.	R.B.C. (mill. per c.mm.).	Hb. (gm. per 100 cc. blood).	Packed red cells (%).	Mean corp. volume (cubic micra).	Mean corp. hemoglobin (micromicrograms).	Mean corp. hemoglobin concentration (%).	Reticulocytes (mill. per c.mm.).	New formed adult R.B.C. (mill. per c.mm.).	R.B.C. with Heinz corpuscles (mill. per c.mm.).	Hemolysis in 0.5% solution NaCl (%).	Opacity of Heinz corpuscles (extinction).
0*	5.8	12.9	42	73	22.4	31	0.10	10	0
1*	4.8	9.6	36.5	74	20.0	26	0.14	..	4.66	31	16
2*	4.6	9.5	35	76	20.6	27	0.18	..	4.42	41	49
3*											
4*	3.0	5.6	26	87	18.7	22	0.54	..	2.46	72	71
5*	2.4	4.5	23	96	18.7	20	0.41	..	1.99	78	66
6	2.0	3.3	19.5	97	16.5	17	0.52	..	1.48	73	57
7	1.6	2.9	17.5	110	18.5	17	0.80	..	0.80	74	45
8	1.4	2.3	15.5	111	16.8	15	1.08	0.07	0.25	54	25
9	1.5	2.7	17	113	18.0	16	1.02	0.32	0.10	36	17
10	1.7	3.3	18.5	109	19.4	18	0.88	0.75	0.07	22	12
11	2.0	4.1	21.5	107	20.5	19	0.64	1.34	0.02	5	8
12	2.7	5.8	29	107	21.5	20	0.81	1.89	0	9	0
14	3.1	7.3	34	109	23.4	21.5	0.59	2.51	0	10	
16	3.7	8.3	36	97	22.4	23	0.30	3.40	0	22	
18	4.3	9.5	39.5	92	22.1	24	0.09	4.21	0	13	
24	5.1	11.5	43	84	22.6	27	0.02	5.08	0	8	
29	4.9	10.9	40	82	22.2	27	0.02	4.88	0	15	
33	5.0	10.7	40.5	81	21.5	26.5	0.02	4.98	0	5	
37	5.8	13.2	45.5	78	22.7	29	0.03	5.77	0	15	

* Acetylphenylhydrazine injections (300 mg.).

3. *Measure of Resistance of Poisoned Red Cells Toward a Hypotonic Salt Solution.* In Chart 3 the percentage of hemolysis observed in hypotonic (0.5%) saline solution during 14 breakdown episodes in 10 dogs is plotted against time. The results indicate that 11 days after the first injection, the behavior of circulating erythrocytes toward this hypotonic solution has again become normal. The fragility of the cells containing Heinz bodies increases with successive pyroquin injections, in some dogs reaching 95% hemolysis on the fifth day. As the new formed cells start to enter the circulation on the third or fourth days after the beginning of the injections, a mingling with the damaged cells occurs, resulting in a progressive return of fragility towards normal from the sixth day on. Since all poisoned red cells (very fragile to hypotonic solution) have completely disappeared from circulation on the eleventh day, the fragility test is again normal at this time.

4. *Quantitative Measure of the Amount of Heinz Corpuscles in Circulation Indicative of Severity of Intoxication.* Chart 4 shows the

the adult erythrocyte. The results presented are an average of the observations made on 7 non-anemic dogs (Nos. 40-213, 37-137, 40-115, 39-194, 40-248, 39-319 and 39-57) and on 2 anemic dogs with depleted iron reserves (Nos. 39-299 and 39-26).

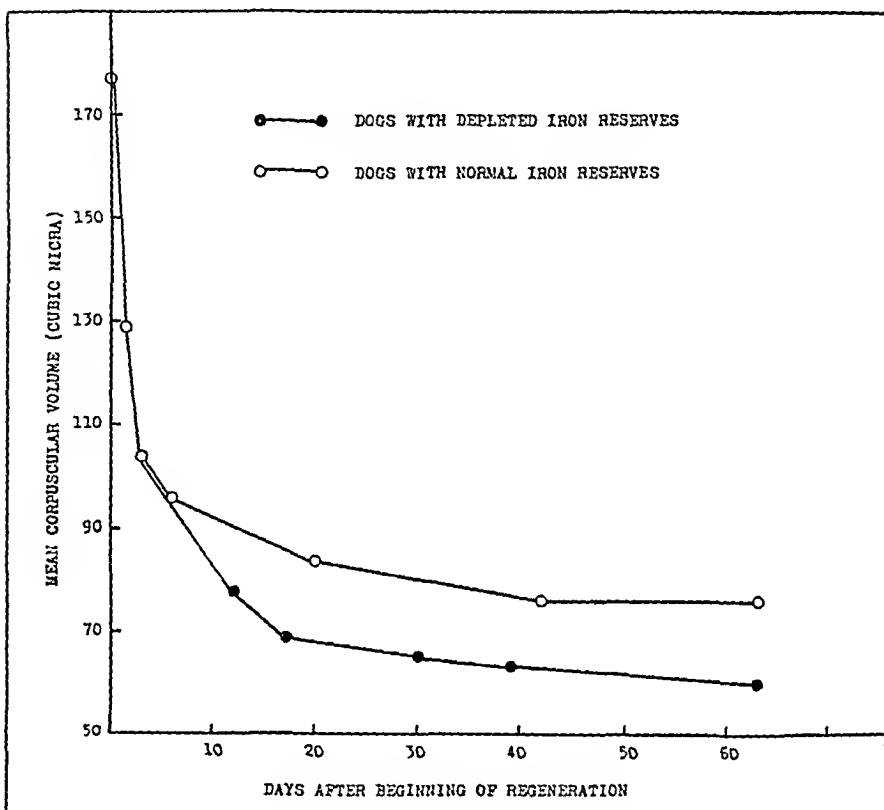


CHART 5.—Mean corpuscular volume changes during blood regeneration following pyridin anemia.

Having determined the following data: (a) mean corpuscular volume of red blood cells with Heinz corpuscles; (b) the mean corpuscular volume of the mixture of reticulocytes and red blood cells with Heinz corpuscles; and (c) the ratio between these two groups of cells, we can then calculate the volume of reticulocytes by the following formula:

$$V = \frac{V_1 \cdot 100 - (V_2 \cdot P)}{P_1}$$

where:

V = Mean corpuscular volume of reticulocytes.

V_1 = Mean corpuscular volume of all red blood cells.

V_2 = Mean corpuscular volume of red blood cells with Heinz corpuscles.

P = Percentage of red blood cells with Heinz corpuscles.

P_1 = Percentage of reticulocytes.

does not represent the maximum reticulocytosis obtainable in this case.

TABLE 3.—HIGHEST RETICULOCYTOSIS OBSERVED AFTER PYRODIN ADMINISTRATION.

Dog No.	Peak of reticulocytosis.		Lowest anemia level, mill. per c.mm.	Number of pyrodin injections.	Amount of pyrodin per kilo of body weight (mg.).
	%.	Mill. per c.mm.			
37-137 (II)	46	0.490	3.2	2	39
40-248	12	0.600	3.4	2	38
37-137 (I)	26	0.730	1.5	3	42
39-299 (I)	32	0.730	1.6	4	67
39-299 (II)	35	0.840	1.3	4	67
40-213	77	1.000	1.4	6	144
39-194	79	1.400	1.7	6	105
40-115 (I)	75	1.100	1.5	8	141
Rabbit No.					
4	88	0.970	1.1	5	80
3	87	1.300	1.0	6	84

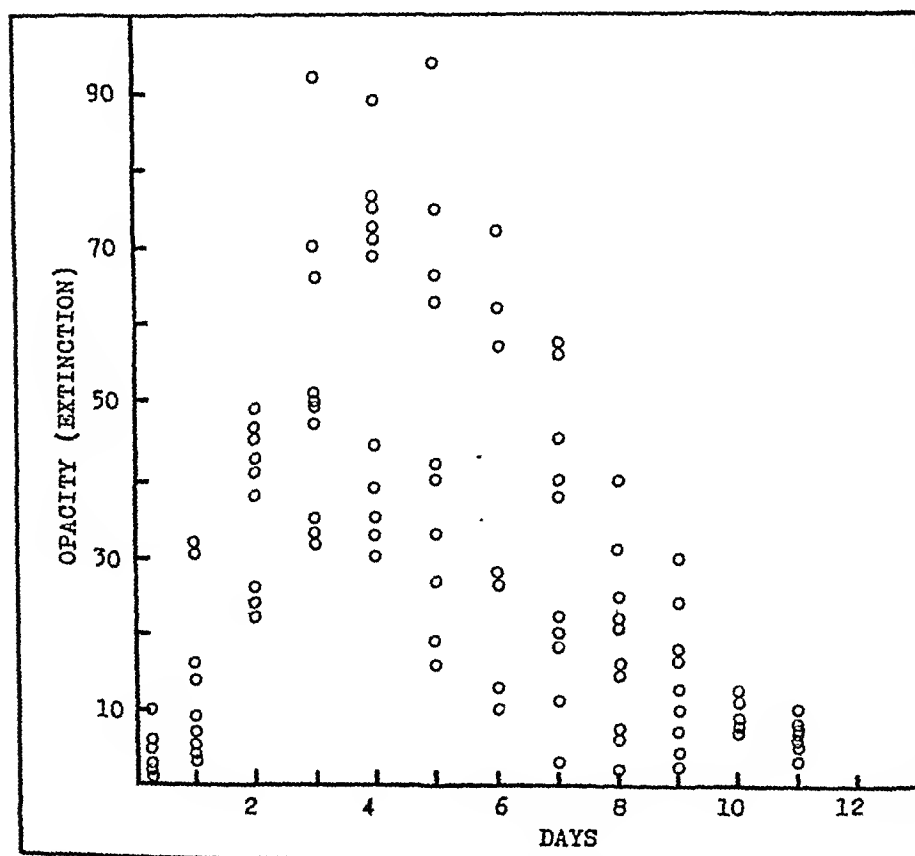


CHART 4.—Measure of turbidity developed by poisoned blood when treated with distilled water. Opacity was measured by light extinction according to the extinction scale of the Klett Summerson photoelectric colorimeter.

6. *Measure of Reticulocyte Mean Corpuscular Volume in Dogs With Normal Iron Reserves and in Dogs With Depleted Iron Stores.* Chart 5 shows changes in volume of reticulocytes in their development to

TABLE 4.—DETERMINATIONS OF NEW FORMED AND DAMAGED ERYTHROCYTES IN PRODIGIN ANEMIA.

Days of observa- tion	Dog 37-137 (II).				Dog 38-290 (I)				Dog 39-299 (II)				Dog 39-191				Dog 40-218				Dog 40-213.							
	(1)		(2)		(3)		(1)		(2)		(3)		(1)		(2)		(3)		(1)		(2)		(3)		(4)			
	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(1)	(2)	(3)	(4)				
0	5.5*	0.01	0		5.8*	0.01	0	7.3*	0.01	0		6.9*	0.01	0		5.4*	0.10	0		6.2*	0.01	0		5.8*	0.10	0		
1	1.9*	0.05	0	1.0	5.0*	0.01	0	5.00	0.01	0	6.50	5.1*	0.01	0	5.39	*				5.7*	0.01	0	5.7	1.8*	0.12	0	4.68	
2	1.0*	0.05	0	3.82	4.3	0.02	0	1.28	*		0				1.0*	0.10	0	3.93	5.3	0.01	0	5.3	1.6*	0.18	0	1.12		
3	3.0	0.10	0	2.91	1.6	0.05	0	1.55	6.0*	0.12	0	5.85	3.9*	0.01	0	3.50	3.6*	0.18	0	3.12				*		0		
4	2.0	0.26	0	1.74	1.0	0.08	0.12	3.80							2.8*	0.67	0	2.13	3.9	0.21	0.08	3.55	3.0*	0.51	0	2.16		
5	1.6	0.40	0.13	1.07					3.1	0.30	0	2.80	2.3	0.18	0.01	2.08	*							2.1*	0.41	0	1.99	
6	1.5	0.33	0.50	0.67	3.6	0.14	0.61	2.81							2.2	0.73	0	1.17	3.5	0.39	0.16	2.05	2.0	0.52	0	1.15		
7	1.7	0.39	1.09	0.22	3.4	0.20	1.10	2.10	1.6	0.31	0.20	0.95			1.7	1.17	0	0.53					1.6	0.80	0	0.80		
8	2.1	0.55	1.55	0.02	3.2	0.16	1.60	1.41	2.1	0.57	0.95	0.55	1.3	0.45	0.57	0.28	1.8	1.12		3.4	0.27	1.00	1.23	1.4	1.08	0.07	0.25	
9	2.8	0.73	2.04	0	3.2	0.19	2.29	0.81	2.3	0.73	1.43	0.24	1.1	0.15	0.93	0.05	1.7	1.19	0.31	0.17			1.5	1.00	0.32	0.18		
10									2.8	0.61	2.07	0.09					1.7	0.63	0.99	0.08	3.5	0.21	2.00	0.36	1.7	0.89	0.75	0.06
11	3.3	0.63	2.67	0	3.8	0.38	3.15	0.27					2.1	0.81	1.56	0.01	1.7	0.60	1.01	0.06				2.0	0.63	1.36	0.01	
12									3.4	0.11	2.91	0.05												2.7	0.81	1.89	0	
13					3.9	0.31	3.60	0.01											0	5.0	0.60	1.10	0					
14	3.7	0.14	3.33	0					4.2	0.12	3.76	0	3.3	0.30	3.00	0	2.4	0.58	1.82	0				3.1	0.59	2.51	0	
15					4.9	0.49	4.11	0																				
16									4.6	0.18	4.12	0												3.7	0.30	3.10	0	
17													4.1	0.16	3.92	0	3.0	0.27	2.73	0								

Column (1) = Total R.B.C., mill per c.mm. Column 2 = reticulocytes, mill per c.mm. Column 3 = New formed adult R.B.C., mill per c.mm. Column (4) = R.B.C. with Heinz corpuscles, mill per c.mm.

* Acetylphenylhydrazine injections

In Chart 5 we can see the rapid change in the mean volume of reticulocytes in the first 3 days of circulation, during which time it decreases from 176 cubic micra to 104 cubic micra. From this point on a difference was observed between anemic and non-anemic dogs. In non-anemic dogs with normal iron reserves the volume of these new formed cells (at this point non-reticulated young erythrocytes) decreases slowly until it reaches normal levels (74 to 78 cubic micra). This occurs between 30 to 40 days after the beginning of regeneration, and does not change appreciably from this level. In anemic dogs, however, with iron reserves depleted by bleeding and kept at low hemoglobin levels for a long period of time before the pyrocin was given, the mean corpuscular volume reached a normal level much earlier (10 to 20 days) and continues to decrease until a microcytic level was reached (58 to 63 cubic micra) identical to that level observed before the drug was given.

7. *Observations on the Maturation of Reticulocytes in the Blood Stream.* During the period in which daily injections of pyrocin were given, all red blood cells appeared as reticulocytes or as erythrocytes containing Heinz corpuscles. Two to 3 days after the last injection another type of erythrocyte was observed in the circulation: a large cell of about the same size as the reticulocyte, undamaged (homogeneous plasma without any granule or vacuole). Some of these cells contained a very small amount of reticular substance while others appeared as complete adult erythrocytes, with no reticulum whatever. This new kind of cell seems to result from the reticulocyte evolution, as indicated by the presence of all types of intermediate stages.

For differentiation purposes we called these cells "new formed adult erythrocytes." At this phase, then, three different kinds of red blood cells were observed: reticulocytes, new formed adult erythrocytes and damaged erythrocytes (red blood cells containing Heinz corpuscles). Table 4 represents quantitative determinations of these three kinds of red blood cells during 7 breakdown episodes in 5 dogs.

8. *Pathologic Examinations.* Sections of some organs have been made in dogs in which death occurred during the red blood cell breakdown period. The anemia was very pronounced in these dogs, 1 day before their deaths; red blood cells ranging from 1.5 to 2 million per c.mm.; hemoglobin from 3 to 3.5 gm. per 100 cc. of blood. In the non-splenectomized dogs (Nos. 40-213, 39-317 and 39-1) we have found large amounts of iron pigment, as well as some intact red blood cells, within the reticulo-endothelial cells of the spleen, liver and bone marrow. The greatest amounts were found in the spleen. In the sections treated with potassium ferricyanide, deposits of intense blue color could be found with intact red blood cells within the same phagocytic cell. This picture was not found very frequently but could be seen without much difficulty. In 1 splen-

damaged by the drug in the treatment of polycythemia vera, as occurs in the experimental anemias related in this paper.

In our experiments the destruction of erythrocytes containing Heinz corpuscles was complete within 9 to 18 days after the first injection. This interval appears to be proportional to the amount of pyrocin administered. It is worth mentioning that the constancy of the rate of destruction is always proportional to the time elapsed after the beginning of intoxication. We were unable to find in the literature figures relating to the destruction of erythrocytes containing Heinz corpuscles. Duesburg,¹³ injecting 77 mg. of pyrocin per kilo into rabbits, obtained a drop in the red blood cell count similar to those observed by us.

There are two different ways to observe the progress of intoxication and consequent disappearance of the erythrocytes: (a) determination of the total amount of Heinz corpuscles; (b) fragility towards hypotonic salt solution. The results show a correlation between the size of the Heinz corpuscles and the fragility toward 0.5% salt solution. Fragility decreases as the total amount of Heinz bodies increases. Following the beginning of regeneration, a progressive number of new red cells are launched into the circulation, these show normal behavior toward hypotonic salt solution and do not contain Heinz corpuscles. During this stage, the blood is a mixture of normal and greatly damaged cells. As the damaged cells disappear, the total volume of Heinz corpuscles tends to diminish and the fragility again becomes normal. This change toward normalcy of the blood occurs between 9 and 18 days following the first injection, as is indicated by the close relationship between three types of observation: 1, morphologic demonstration of Heinz bodies by means of direct microscopic examination; 2, determination of the amount of Heinz corpuscles by nephelometric method; 3, behavior toward hypotonic salt solution.

The lack of any appreciable amount of free hemoglobin in the plasma and the progressive disappearance from the circulation of erythrocytes containing Heinz bodies, seems to indicate a slow, continuous removal of these damaged cells as *whole* cells from the blood stream. Long²³ and Alcock¹ demonstrated erythrophagocytosis in this type of anemia. We have confirmed these observations and were impressed with the intensity of this phenomenon. In order to demonstrate that the enormous amount of iron pigment found in the reticulo-endothelial cells is the result of phagocytosis of the red blood cell and not of free hemoglobin, we sacrificed a rabbit 24 hours after the first injection of pyrocin. We expected to find a greater number of intact erythrocytes in the reticulo-endothelial cells. The expected picture was not seen, probably because the hemoglobin of the phagocytized erythrocytes was rapidly converted into bilirubin with consequent deposition of iron as shown in experiment done in dogs with gall-bladder renal fistula.¹⁰ In these dogs there

ectomized dog we observed (No. 39-152) a considerable increase in the size of Kupffer cells in the liver and reticulo-endothelial cells of the bone marrow. All of them contained large amounts of iron pigments and some phagocytized erythrocytes.

Discussion. *Blood Destruction.* In studying the mechanism of the action of hydrazine derivatives upon the blood, it is of paramount importance not to compare results obtained with different drugs, or different amounts of substances, or, finally, with different methods of administration. For instance, Itoh,²¹ with 10 to 50 mg. of phenylhydrazine hydrochloride given intravenously in dogs, obtained a drop from 7 million red blood cells per c.mm. to less than 1 million in 24 hours, with massive hemolysis in the serum. Alcobe,¹ giving 10 mg. of phenylhydrazine hydrochloride per kilo body weight (no information about the method of administration), obtained massive hemolysis. Formation of methemoglobin is described by Dreschfeld¹² and some other authors. We found a similar picture in 1 dog (No. 39-262) into which we injected subcutaneously a massive dose of 2 gm. of pyrocin in one single injection. This dog died 5 days after the injection.

When one employs, however, non-lethal doses of a hydrazine derivative, quite a different picture is obtained. Massive hemolysis in the blood stream with the presence of free hemoglobin in the plasma is not demonstrable but one may see very slight traces during the beginning of the intoxication. We observed a marked tendency to spontaneous hemolysis *in vitro* with intoxicated red cells. To demonstrate hemoglobinemia properly it is important that the blood be centrifuged as soon as possible following removal from the body. Even in these cases, at times one may observe a small layer of hemolysis in the upper part of the packed red cells in the hematocrit tube. In some cases 10 to 15 minutes at room temperature is sufficient to produce some degree of hemolysis.

A characteristic finding of that type of intoxication pointed out by Heinz^{20a,b} is the presence of a refractile granule in the red blood cells. This author observed the same phenomenon when using other hydrazine derivatives. Certain properties of these Heinz bodies have been described by Hartwick¹⁸ and a detailed chemical analysis has been made by Kunkle.²² We have confirmed the presence in these of very minute amounts of iron. Furthermore, we observed the non-formation of these bodies in the reticulocytes; a rough determination of its volume during the most acute phase of intoxication as well as the determination of the total amount of Heinz bodies (nephelometric method) during different phases of the poisoning.

In the most important papers concerning treatment of polycythemia vera with hydrazine derivatives, we were unable to find any reference to the presence of Heinz corpuscles.^{2,3,14,15a,b,c,16,24,25,29-31} It seems important to us to know whether all the erythrocytes are

cytosis is obtained with anemias produced by hydrazine derivatives. Does this mean a more violent regeneration than other types of experimental hemolytic anemias, as produced for example by intravenous injections of distilled water? We believe that the percentage of reticulocytes is much higher than in other types of anemia, because with hydrazine anemia we have a progressive concentration of reticulocytes in the blood due to the fact that destruction occurs only in non-reticulated cells. The resistance of the reticulocytes to the drug makes these cells immune to damage, while on the other hand the adult red cells are rapidly disappearing from the blood stream.

However, it is not only a high percentage of reticulocytes that one observes in this anemia, but also a truly great increase in their total number. In Table 3 it is shown that the highest absolute numbers are obtained with a large number of injections, while lower values are obtained only when a few injections have been given. Table 4 indicates that when 6 injections have been administered (Dogs 31-194 and 40-213) there resulted 1.42 and 1.08 million reticulocytes per c.mm. before any evolution toward adult erythrocyte was observed. This seems to indicate either a paralyzing property of pyrocin in the maturation phase reticulocyte—adult erythrocyte, occurring in the blood stream, or a hindering property on the bone marrow capacity to form complete adult red cells. As is indicated in Table 4, maturation of reticulocytes always occurred between 48 and 72 hours after the last injection. This constancy could perhaps be interpreted as one more indication that the span of the reticulocyte stage is of that order of magnitude. If we consider that the reticulocytes are still subjected to the drug for a certain period of time following the last injection, it is quite possible that the maturation time in physiologic conditions might be around 24 hours, as observed in humans by some authors.^{11,19,27,28}

We believe that this type of anemia would give greater information concerning the duration of the reticulocyte stage in the blood stream if careful morphologic observations were made at short intervals (12 hours) during the period of regeneration. In this way quantitative data could be obtained regarding the transformation of the reticulocyte into a newly formed adult erythrocyte. Also the question as to whether the red cell always leaves the bone marrow as a reticulocyte or also sometimes as a complete adult erythrocyte under normal conditions could perhaps be elucidated by this experimental anemia.

Summary. The administration of pyrocin produces no marked differences in the destruction and regeneration of erythrocytes between normal, splenectomized, renal fistula dogs and those with severe hypochromic anemia.

Destruction Phase. 1. In dogs or rabbits all red blood cells other than reticulocytes are damaged 24 hours after injection of pyrocin, as shown by the presence of Heinz bodies in the cells.

was a marked increase of bilirubin output in the urine eliminated during a 24-hour period following the first injection. Our interpretation of phagocytosis as the main mechanism of destruction in this type of anemia is based upon the frequent finding of red cells within reticulo-endothelial cells containing iron pigment as well.

Blood Regeneration. The reticulocytes increase in number between the third and fourth days following the first injection. The number of new cells formed each day appears to be quite constant, at least for the 10 first days of the regenerative period. As we³ and Bodansky⁴ have observed during treatment of hookworm anemia and other hypochromic anemias, the reticulocytes have a greater volume than the adult erythrocytes. Bodansky and Dressler⁵ found an increase of the water content in the reticulocytes as compared with adult erythrocytes. An approximate idea of the mean corpuscular volume of the reticulocytes as presented in this paper, indicates a volume twice that of the adult erythrocyte. The evolution of the reticulocyte toward the adult erythrocyte seems to be accompanied by a rapid decrease in mean corpuscular volume. A modification of its shape must also occur if we take into consideration the result obtained in a recent study⁹ of the fragility in hypotonic solutions of new formed cells tagged with radioactive iron. This interpretation is based upon the widely accepted explanation of the mechanism of hemolysis toward hypotonic solutions, emphasizing the relationship between the shape of red cells and their behavior in hypotonic solutions.^{7,17,26}

The amount of hemoglobin in the reticulocytes seems to be the same as that in adult erythrocytes, thus indicating a lower hemoglobin concentration for the reticulocyte as compared with the mature erythrocyte.

In animals rendered anemic by bleeding, erythrocytes are microcytic and poor in hemoglobin. In these animals the regeneration following hydrazine shows the presence of reticulocytes of the same size and hemoglobin content as observed in reticulocytes of a normal dog. This finding indicates a normal capacity to form red cells in such conditions. If this takes place during the physiologic formation of new red cells in this type of anemia (hypochromic, microcytic) it might indicate that the erythrocytes become smaller and hypochromic in the blood stream through loss of hemoglobin while in the circulation. It is surprising to note how great the difference in the distribution of hemoglobin is before and after administration of hydrazine. For instance, in anemic Dog 39-299, 7.4 gm. of hemoglobin per 100 cc. of blood was distributed among 6.5 millions R.B.C. per c.mm. In contrast, during the regenerative phase following the administration of pyrocin, we found the same amount of hemoglobin (7.4 gm.) distributed among only 3.4 millions R.B.C. per c.mm., *i. e.*, half the number of erythrocytes found previously.

It is a well-known fact that the greatest experimental reticulo-

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RESULTS OF CHEMOTHERAPY IN SUBACUTE BACTERIAL ENDOCARDITIS.

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LICHTMAN and Bierman⁶ have recently assembled the reported largest series of experiences in the treatment of subacute bacterial endocarditis with sulfonamide drugs. Among 198 cases receiving simple chemotherapy there were 12 (6%) recoveries. Among 89 other cases in which such chemotherapy was combined with other measures—intravenous heparin, physically induced hyperthermia, intravenous typhoid vaccine or radiotherapy—there were 14 (16%) recoveries.

It is our purpose to add to these reports the experiences in the treatment of 36 cases of subacute bacterial endocarditis in this hospital who received one of the sulfonamide drugs for more than 1 week, more than 2 weeks before death. Among these were 1 probably proven case with recovery and 1 death with cerebral hemorrhage in a patient who was receiving continuous heparin administration.

Several patients received more than one sulfonamide drug; 23 received sulfapyridine; 13 received sulfanilamide; 7 received sulfathiazole; 4 received sulfanethylthiazole; 1 received neoprontosil and 1 received sodium paranitrobenzoate.

2. Damaged cells became progressively more fragile in 0.5% NaCl solution in distilled water.

3. In a given anemia the Heinz bodies increase in size with the severity of intoxication that follows repeated doses; the Heinz body is larger in the severely intoxicated animal than in one less severely intoxicated. Heinz bodies produce increased turbidity when blood is laked in distilled water.

4. Damaged cells disappear progressively and completely from the blood stream in 12 days, on the average, after beginning the poisoning. Evidence for this is obtained by direct morphologic examination; by return to normal behavior toward hypotonic salt solution, as well as by disappearance of the turbidity of distilled water due to insolubility of Heinz bodies.

5. Doses of pyrocin employed did not cause appreciable hemolysis (as seen by the appearance of the plasma) throughout the intoxication process.

6. Pathologic examinations of animals sacrificed or dead at different stages of the intoxication showed large amounts of iron pigment and some erythrophagocytosis in the spleen, liver and bone marrow.

7. The mechanism of destruction in this type of anemia apparently acts primarily by damaging erythrocytes. These cells become like foreign bodies and are phagocytosed by cells of the reticulo-endothelial system.

Regeneration Phase. 1. The regeneration begins 3 to 4 days following intoxication and is maintained for 10 to 15 days at a high rate, putting into circulation on the average 0.300 million R.B.C. per c.mm. daily.

2. Mean corpuscular volume of reticulocytes could be roughly estimated as double that of adult erythrocytes.

3. It has been shown that dogs with severe microcytic, hypochromic anemia could produce reticulocytes with normal mean corpuscular volume, containing normal amount of hemoglobin, during regeneration after pyrocin anemia. However, microcytosis could be again observed after some time.

4. If all erythrocytes leaving the bone marrow are reticulocytes, then pyrocin seems to have a paralyzing effect on the maturation of reticulocytes to normal adult erythrocytes. This fact, together with the specific destruction of adult red blood cells, seems to explain the high percentage of reticulocytes in this type of anemia.

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following which there was a daily maximum of 99° to 99.5° (oral) until the 20th hospital day. The patient then had a severe chill with a fever of 105° (rectal). Thereafter, he had an intermittently high fever with chills until chemotherapy was started. On the 22d hospital day there was tenderness in the left upper quadrant. On the 25th hospital day he had pain in the right forearm over the tendon of the flexor digitorum without signs of inflammation.

When the blood cultures were found to be positive, treatment with sulfapyridine was started. After a period of 8 days, during which time some doses were omitted or reduced because of toxic symptoms, he was able to tolerate alternating doses of 1 gm. and 0.5 gm. of sulfapyridine every 3 hours. After the institution of chemotherapy there was a reduction of fever to a daily maximum of 99° to 99.5° (oral) until the 36th hospital day, when it rose to 102.2°. It remained at approximately this level for 48 hours. Then sulfapyridine was discontinued. The temperature gradually subsided to normal in the next 2 days and remained normal thereafter. The patient has remained in his usual state of health for 16 months.

CASE 2.—J. T., a 29-year-old white nurse, admitted to the hospital on February 3, 1940, had been well until October, 1939, when she developed anorexia, fatigue, a mild dry evening cough, and drenching nightsweats. She continued her nursing duties until 6 weeks later, when she had a sudden attack of severe epigastric and right upper quadrant pain with vomiting and persistent nausea. After a week's rest in bed she returned to work, but complained of increasing fatigue, transient arthralgias, and evening temperatures ranging between 99.2° and 100.8°. Within the last month she had also had an attack of left-sided pleurisy lasting a few hours, another "gallbladder" attack, and an episode of pain, redness, and swelling in the left ankle which had subsided after a few days without residual. Since the onset of her illness she had lost 13 pounds.

She gave no history of dental extraction or infection shortly prior to her illness. No disturbance of the menstrual cycle was reported. She had been in the habit of expressing the contents of small acne pustules on the face.

She had had frequent tonsillitis and "growing pains" as a child. Her tonsils had been removed at the age of 14 "because of a bad heart." In 1936, at a preemployment examination, she was told that she had rheumatic heart disease with aortic insufficiency and the examiner at that time remarked on the presence of clubbed fingers.

Physical Examination. The patient appeared pallid and chronically ill. Acne vulgaris was present over the face and shoulders. The left border of cardiac dullness was 9.5 cm. to the left of the mid-sternum. At the cardiac apex there was a systolic thrill and a loud, rough systolic murmur. The diminished aortic second sound was succeeded by a high-pitched, blowing, early diastolic murmur. The pulse rate was 110, regular, and of the Corrigan type. Her systolic blood pressure was 80 mm. Hg; diastolic, 46. The liver edge was palpable, 5 cm. below the costal margin in the mid-clavicular line on moderate inspiration. The spleen could not be felt. There was definite clubbing of the fingers. No petechiae were noted. Pelvic examination revealed no abnormality.

Laboratory Data. All urine examinations were negative. Hemoglobin was 60% (Sahl); red blood cell count was 3,300,000 per c.mm.; and the white blood cell count was 12,550 with 76% neutrophils. The Kahn test on the blood serum was negative.

Three successive blood cultures showed up to approximately 150 colonies per cc. of *Staph. albus*. The orthodiagram revealed generalized cardiac enlargement. An electrocardiogram showed slight left axis deviation.

Treatment with sulfamethylthiazole, 1 gm. every 6 hours, was commenced on the 6th day of hospitalization. In 2 days the temperature had fallen to

As has been a common experience, particularly during the administration of sulfapyridine, there was frequently a subsidence of fever without apparent effect on the course of the disease. With the exceptions to be noted, the temperature never remained completely normal for more than a very few days. The antipyretic effect of sulfapyridine has been noted by other observers.¹

When colony counts were done, there was commonly a decrease in the number of organisms demonstrated in the blood stream. Five patients had one or more negative blood cultures during chemotherapy while they continued to be febrile. These were probably falsely negative cultures. Janeway,⁴ in reporting a method to avoid such falsely negative blood cultures, remarked on the inhibiting effect of previous exposure of organisms to sulfanilamide and of the sulfanilamide present in the blood sample upon the growth of a small number of organisms.

Three patients had complete remissions of fever with repeatedly negative blood cultures for 18 days, 19 days, and 2 months, respectively. One of these was the case with cerebral hemorrhage, to be described. The other 2 relapsed and died in spite of continued chemotherapy.

Case Reports. CASE 1.—W. P., 23-year-old male student, was admitted to the hospital on October 15, 1939. Two years previously he had received here the diagnoses of congenital heart disease, tetralogy of Fallot, moderate cardiac enlargement, right bundle branch block and fair exercise capacity.

For 1 week he had noted gradually increasing ease of fatigue and aching of the back and legs. Four days before admission he had two episodes of sharp pain in the right paraumbilical region, followed by a mild residual pain. On the morning of admission he experienced a sudden, severe pain in the lower anterior chest, on both sides, which was greatly aggravated by inspiration. During that day he had eight shaking chills.

Physical Examination. The patient appeared to be acutely ill, in distress, and was deeply cyanotic. Respirations were shallow and rapid. No abnormal pulmonary signs were detected. The apex impulse was in the fifth interspace, 8 cm. to the left of the mid-sternum. There was a pronounced systolic thrill over the precordium, most prominent over the upper left portion of it. A loud harsh murmur with similar location of maximum intensity almost completely obliterated the first heart sound. It was transmitted well over the anterior chest and but slightly to the neck vessels. There was mild tenderness in both costovertebral angles and over the right side of the abdomen. There was marked clubbing of the fingers and toes.

Laboratory Data. Roentgen rays of the chest on the 2d, 10th, and 20th hospital days showed no evidence of a pulmonary lesion. Eleven of 16 urinalyses showed a trace or more of albumin. On the 22d and 23d hospital days there were 10 to 15 red blood cells per high power field in the centrifuged urinary sediment. The white blood cell count was 10,500 and remained at that level until the third week of hospitalization, when it ranged between 12,000 and 13,500. Hemoglobin was 150% (Sahli). The red blood cell count was 8,770,000. Four blood cultures in the first 3 weeks showed no growth. *Strep. viridans* grew in the blood cultures taken on the 20th and 21st hospital days. Subsequent blood cultures showed no growth.

Course. During the first 36 hours the temperature varied between 102° and 104.5° (rectal). Then there was an abrupt drop in the temperature

to eradicate the infection localized in the vegetations and in infected emboli. The absence of relapse in Case 1 after chemotherapy had been discontinued because of drug fever may have been due to lack of time for large enough vegetations to form to protect the organisms from the sulfapyridine. It seems probable that chemotherapy should be continued for a long time, in most cases, in order to destroy all of the organisms in the vegetations.

We have not obtained, even temporarily, sterilization of the blood as frequently as has happened in most reported series. As more sulfonamide drugs become available it will probably be desirable to select the drug on the basis of the bacteriostasis demonstrable *in vitro* for the strain of organism cultured from the individual case. Swain⁷ reported a marked variability in the susceptibility to sulfapyridine of four strains of *Strep. viridans* isolated from cases of subacute bacterial endocarditis. There was good bacteriostasis of two strains from patients whose blood streams became sterile and no bacteriostasis was demonstrated with two strains from patients whose bloods were not sterilized by treatment.

Kelson and White,⁵ in their original report, recognized the danger of excessive bleeding incident to embolism in the treatment of subacute bacterial endocarditis with heparin. They reported one case who died with large occipital and subdural hematomas. These were considered to be embolic but it was thought that the heparin probably increased the hemorrhage. Other cases dying with cerebral hemorrhage during heparin treatment have been reported by Friedman, Hamburger and Katz,³ Witts⁹ and by Fletcher.² The latter noted that in all of these cases sulfapyridine had failed to sterilize the blood stream. He suggested that the persistence of a positive blood culture, and in particular the continued appearance of embolic signs, should contraindicate heparin treatment. Kelson and White⁵ had advised beginning heparin administration from 4 to 7 days after sulfapyridine had been started. If a sterile blood stream is to be a prerequisite for heparin treatment, some method such as that proposed by Janeway⁴ should be used to avoid the falsely negative blood cultures which we and others have obtained. In our Case 2, the continuously normal temperature obtained suggests that the blood cultures were truly negative but that this did not prevent the occurrence of emboli. Four other patients in this series, whose blood was not sterilized, received continuous intravenous infusion of heparin during 10- to 15-day periods, without accident. In Case 2, more heparin was used and the clotting time was prolonged more than advised by Kelson and White.⁵ We have found considerable individual and day-to-day variation in the effect of heparin on clotting time. It had required considerably larger amounts of the same lot of heparin in a previous patient to prolong the clotting time to the desired value.

normal from its previous range of 100° to 103° (oral), and it remained so for the remaining 20 days of hospitalization. The white blood count continued between 10,000 and 13,000. Blood cultures became decreasingly positive, and on the 12th, 14th, and 16th days after the commencement of the therapy they showed no growth. A final blood culture, taken 5 days later, was positive.

Throughout the period of observation the patient complained of transitory pains under the nails, but no petechiæ were seen. On the 18th hospital day a small, red, painful area appeared at the base of the big toe. On that day was started continuous intravenous administration of heparin. In 18 hours she received 44,000 units of heparin, and her clotting time by the method of Lee and White had risen from 13 minutes to 2 hours, 25 minutes. At this time she had a severe epistaxis, became very nauseated and vomited about 75 cc. of coffee-ground material. At about the same time she began to complain of a severe generalized headache and numbness of the hands. All treatment was stopped immediately. The headache persisted, the numbness became localized in the left hand which showed motor incoördination. She remained much prostrated and died suddenly in the night, 1 week after heparin had been discontinued.

Autopsy. The heart weighed 490 gm., and the left ventricle was hypertrophied. Microscopic examination revealed some interstitial myocardial fibrosis, but no typical Aschoff bodies. There were a few vegetations on the mitral valve which was not greatly deformed. The aortic leaflets were thickened, adherent, and covered by vegetations. The largest lesion was on the valve cusp beneath the left coronary ostium, and measured 5 mm. in diameter. A smear and a culture from the center of the vegetations showed an abundance of *Staph. albus*.

In the spleen were three small infarcts. In the fundus uteri were some small remnants of hyalinized placenta, which were not infected. There was a recent thrombosis in the large veins of the broad ligaments.

On the middle portion of the superior aspect of the right cerebral hemisphere there was an area of old hemorrhage, measuring 6 by 8 cm., in the subarachnoid and penetrating the superficial layers of the cortex, within which a zone of fresher hemorrhage about 1.5 cm. in diameter could be seen. Microscopic examination revealed an organizing embolus in a large superficial artery with fresh hemorrhagic necrosis in the center of the infarcted area and older, ischemic necrosis and reactive gliosis about the periphery of it. This was interpreted as evidence of a previous infarct, several days old, undergoing necrosis, into which a fresh hemorrhage had occurred.

Comment. The diagnosis of subacute bacterial endocarditis in Case 1 was fairly well established by the two positive blood cultures on consecutive days, the pleuritic pain without development of demonstrable pulmonary lesions (the congenital heart lesion would permit pulmonary embolism), transient microscopic hematuria and episodes of abdominal pain and tenderness. It is probable that the early treatment, 1 month after the first fatigue symptoms, perhaps before organisms were buried deeply in vegetations, was a factor in the favorable result. In Case 2, the persistence in vegetations of organisms of low-grade virulence and good susceptibility to chemotherapy (*Staph. albus*) when the temperature had been normal for 3 weeks and 3 blood cultures had been negative, illustrates the difficulty in the chemotherapy of subacute bacterial endocarditis.

Temporary sterilization of the blood stream cannot be expected

1932, Foshay^{8a} first reported on a serum treatment for this disease. This was followed by a number of other contributions^{8b-c} on the same subject, the latest being a statistical study of 600 cases in which serum treatment^{8f} was used. His early remarks as regards these 600 cases are that "the results of serum treatment varied considerably, especially with relation to the clinical type that was presented, the presence or absence of extensive visceral lesions, the quantity and potency of serum that was given, and the stage of disease at which patients were treated." In a further analysis of these cases Foshay states that "statistical studies confirmed and, in some respects, amplified the clinical evidence that serum therapy modified favorably the course of the disease with respect to morbidity and to mortality."

Baer¹ reported the early use of small doses of Roentgen rays to the primary lesion in 2 cases resulting in the arrest of the progress of the disease. Bate,⁴ in 1934, used the blood of a patient who had recovered from tularemia, giving it as a transfusion, with gradual improvement. Elson,⁶ using the syrup of ferrous iodide, reported rather enthusiastically on 2 cases. He feels "that ferrous iodide is a specific in tularemia." Barthelme³ has used metaphen successfully in the treatment of this disease, reporting 60 cases with 1 death. He reports that Shelton has used quinine successfully.

Sulfanilamide and its derivatives have received much attention in the past 3 years in the treatment of tularemia. Miller and Bannick,¹⁰ reporting a case, used heavy doses of sulfanilamide over a period of 6 days with apparently no benefit. This patient showed a "prompt improvement" following the use of 2 doses of Foshay's antitularemia serum. Powers and Powers¹² later reported recovery of a case following the use of sulfanilamide and Foshay's specific antiserum. Curtis^{5a} reported the successful treatment of a case with sulfanilamide; and this was followed by a report^{5b} of 4 additional cases similarly treated. Weilbaecher and Moss¹³ report 5 interesting cases of tularemia treated with sulfapyridine, sulfanilamide, sulfamethylthiazole and sulfathiazole. Their observations were such as to show benefits only with sulfamethylthiazole and sulfathiazole. Johnston reported a very unusual case in which "rapid clinical improvement ensued immediately following the use of sulfanilamide." However, "during the subsequent rise in fever the drug was purposely withheld, in spite of which a prompt drop to normal occurred." From this observation he inferred that "one cannot know whether sulfanilamide was of any value or not." Barkley,² after using large doses of sulfanilamide for 5 days without any results, changed to sulfathiazole in large doses for 4 days with a clearing up of symptoms 48 hours after the latter drug was started.

From the above reports it is readily apparent that the treatment of this disease is still very uncertain. Since December 27, 1940, the writer has had occasion to treat 3 cases of tularemia. One of these

Staph. albus as the infecting agent in subacute bacterial endocarditis is uncommon, occurring in 4 of Thayer's⁸ series of 362 cases. There has been one other case due to this organism in this hospital in the last 15 years. In one of Thayer's cases, the origin was ascribed to a paronychia. In our case, possible sources were traumatized acne postules or previous uterine infection.

Summary and Conclusions. Among 36 cases of subacute bacterial endocarditis treated with sulfonamide drugs there were 5 cases with one or more probably falsely negative blood cultures, 3 instances of probable sterilization of the blood stream with normal temperature temporarily and 1 cure of a probably proven case. Among 5 cases who also received continuous intravenous infusion of heparin there was 1 death with cerebral hemorrhage and no cure.

The reported experiences in the chemotherapy of subacute bacterial endocarditis warrant persistence in the accumulation of data concerning the different adjuncts to chemotherapy and the selection of a sulfonamide drug on the basis of bacteriostasis, demonstrable *in vitro*, for the strain of organism obtained from the individual case.

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THE TREATMENT OF TULAREMIA WITH ACRIFLAVINE.

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THE treatment of tularemia continues to be very uncertain in spite of reports on successfully treated cases appearing in the literature from time to time. Perret,¹ reporting a study of 69 cases, is of the opinion that the treatment of this disease "is symptomatic." Since the introduction of sulfanilamide and its various derivatives, an increasing number of cases, treated with these drugs, is gradually appearing in the literature. Certain it is that even at the present time many types of therapy continue to be used, and these usually with most uncertain results.

Fisher⁷ reported successfully on the use of neoarsphenamine in the treatment of 4 cases. Most writers, however, feel this drug to be ineffective and have accordingly discontinued its use. Early in

Upon leaving the hospital he felt badly and very weak; which continued for many days. At times he felt fairly well, but usually he was tired, lazy, droopy and restless. He was never able to return to work.

On January 23 a painful tooth was extracted. The following day he again developed high fever, with pains over his entire body, free sweating and had several chills. The right axillary mass became more painful, and after several days of self-medication he called me in (January 27), and I sent him to the hospital. The agglutination test for tularemia was reported as positive.

On January 30 acriflavine was given, as in Case 1. The next day the fever dropped to normal and remained so for 2 days, when, following another intravenous administration of acriflavine, it went to 100° for a short time. After this it never went higher than 99.4° F., which followed a third treatment with acriflavine on February 5. He was permitted to go home on the following day.

After the first administration of acriflavine, the patient said he felt markedly improved. His malaise disappeared completely and his strength seemed to return overnight. His appetite became very good, and he frequently asked for second servings. He showed signs of a returning ambition and was anxious to go back to work. His general appearance markedly improved, and pallor was soon replaced by a rosy complexion. When seen in the office 4 days after leaving the hospital he said he felt "a thousand times better." The pain in his right axilla had disappeared after the first administration of acriflavine. On February 27 he was working and feeling fine. He had regained much of the weight he had lost, and had never had any more trouble.

CASE 3.—Mr. A. B., aged 21, began cleaning rabbits in large numbers, when the season started, with the above Mr. J. M. At about 2 A.M. on November 26, 1940, the patient was awakened by a chilly feeling and continued having chills all night. In spite of feeling very badly, he forced himself to go to work. Although he felt much depressed and uncomfortable, he had no pains. The condition was diagnosed and treated as influenza, but as he was no better by November 30, he went to the Charity Hospital. On November 29 he first noticed a small painless mass in his left axilla.

At the hospital a small lesion, that had been present several days, was discovered proximal to the nail base on the dorsal aspect of the left middle finger. A diagnosis of tularemia, ulcero-glandular type, was made and he was admitted. The agglutination test for tularemia was positive. Here he was treated with large doses of sulfathiazole. He was discharged on December 29.

On leaving the hospital he continued to feel badly and had an occasional chill. His family physician incised and drained much pus from large left epitrochlear and left axillary lymph nodes (about February 19). He continued running a low-grade fever.

I first saw him on March 10, and sent him to the hospital on the following day. During his 12 days there he was given 4 intravenous treatments of acriflavine administration in the same manner as for the above 2 cases—the administrations being given every 72 hours. Following these treatments he said he felt much stronger and his appetite returned. Although he continued to run a low-grade fever at irregular intervals, he was permitted to go home, in the hope that the fever would soon subside entirely, and he would recover fully. In spite of the moderate clinical improvement, however, he continued to run this low-grade fever; and on April 7, a check-up examination showed a moderately enlarged liver and a definitely palpable spleen. The epitrochlear sinus had stopped discharging in the hospital, but the axillary sinus continued draining slightly. On April 9, as the spleen seemed larger, he was referred to Drs. Menville and Ané, who subjected

cases was acute and the other 2 definitely chronic. Because of an interesting experience with acriflavine in the treatment of a case of typhus in May of 1940, I decided to use this drug on these cases. It is my intention in this report, therefore, merely to present the histories of these 3 cases of tularemia in which this drug was used apparently with distinct benefit. Although I do not make any claims for any form of therapy on the basis of 3 cases, nevertheless, the results obtained, I believe, adequately justify the presentation of this subject, in the hope that additional investigations might determine its true value.

Case Reports. CASE 1.—Mr. N. F., aged 21, a worker in the fish and game market, became ill on Christmas Day, 1940. He had returned home late from a Christmas Eve party feeling well. When awakened at 3 in the afternoon, he had a headache, and felt badly. From this time until December 29, when he first noticed he was in a hospital, he remembered nothing at all. A history from the family showed he had been skinning rabbits for 2 months, the last being on December 24. His temperature was slightly over 105°. He was incoöperative and talked incoherently. Examination of his hands showed a small ulcer about 3 mm. in diameter on the dorsum of his right index finger over the distal interphalangeal joint. The right axillary lymph nodes were enlarged, very tender and painful. A diagnosis of tularemia was made and he was sent to the hospital. An agglutination test for tularemia on January 2 showed "a few clumps in a dilution of 1 to 20." On January 7, the test was positive at 1 to 320.

Until January 3, he was treated symptomatically. Sulfathiazole and neoarsphenamine were next used. On January 11, he was given 100 mg. of acriflavine, dissolved in 250 cc. of normal saline, intravenously. This was followed by 1000 cc. of 5% glucose in normal saline as an infusion. In the afternoon of this day the patient said he felt "fine." His temperature for the first time failed to go above 100° F. The next day there was a very marked improvement in his clinical condition. He volunteered the information that he was feeling fine for the first time since becoming ill. His pains were all gone. The enlarged and painful right axillary lymph nodes seemed to suddenly become painless. The maximum temperature on January 12 was 99.6°. By noon of this day it dropped to 99°, reaching this level again the following morning and at 8 P.M. on January 14. During the afternoon of this latter day, another 100 mg. of acriflavine was given. The next morning the temperature was 98 and never again went above normal. His strength seemed to return so rapidly, and he felt so greatly improved that he wanted to go home the next day. He left the hospital on January 19.

On February 11, the patient felt strong and entirely recovered from his illness. He had gained about 10 pounds; and the enlarged axillary lymph nodes were still painless and seemed to be getting smaller. The region of his primary lesion showed a darkly pigmented, small scar.

CASE 2.—Mr. J. M., aged 27, a market worker, had been cleaning rabbits since the season started. On the morning of December 11, 1940, he awakened with chills and fever. All day he felt chilly at work and that night began having pains all over his body. Continuing to feel "miserably," and now having pain in right axilla, he called in a physician on December 13, who sent him to the Charity Hospital with the diagnosis of "rabbit fever." The primary lesion was found on the volar surface of his right index finger, over the distal interphalangeal joint. The agglutination test for tularemia was positive (1 to 320) on December 28. He was treated with large doses of sulfathiazole and on December 30 was permitted to go home.

well established until acriflavine was administered. In the third case the drug had eventually to be given more frequently in order to have a definite inhibitory influence on the growth of the offending organism.

Conclusions. 1. The treatment of tularemia is briefly reviewed.

2. Though the writer has had no experience with the use of Foshay's antitularemia serum, the results from its use, as reported by Foshay himself, do not seem to have been sufficiently impressive to warrant its routine employment in all cases.

3. Sulfanilamide and its derivatives are of little, and probably of no value in the treatment of this disease.

4. Histories of 3 cases of tularemia are herein presented. The use of acriflavine intravenously seems to have been of distinct benefit in the treatment of each. The writer agrees that further observations in the use of this drug in the treatment of tularemia are necessary before making any definite evaluation of its efficacy.

5. Should acriflavine prove to be of distinct benefit in the treatment of tularemia, it will very probably be shown that its action is bacteriostatic, permitting the host time to build his defense against this infection.

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THE LOCAL TREATMENT OF PYOGENIC CUTANEOUS INFECTIONS WITH SULFATHIAZOLE IN AN EMULSION BASE.*

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INFECTIOUS dermatoses of various types offer an inviting field for treatment by the local application of sulfonamide compounds. In

* This study was aided by a grant from the Smith, Kline & French laboratories.

his spleen to 4 Roentgen ray treatments. The organ diminished in size; an epigastric discomfort passed off; and in spite of some discomfort after each treatment, an apparent improvement was admitted by the patient.

Despite this, however, he continued running fever, and by April 14, the fever began going over 100° F. Foshay's serum was considered, but the cost could not be afforded. I then decided to keep him at absolute rest in bed, treating him symptomatically at his home. After nearly 10 days as no improvement was observed, I decided he should reënter the hospital for more intensive treatment with acriflavine.

On April 28 he was admitted to the French Hospital, where he remained until May 18. Another agglutination test for tularemia was reported positive. During this time he was given 8 intravenous administrations of acriflavine according to the usual method (April 29 and 30, May 1, 3, 5, 7, 10 and 14). After his second treatment he said he felt very much better. His strength seemed to return, his appetite improved, and he was able to rest better. Each administration of acriflavine was followed by a slight rise of not more than 1° of fever, except the last, which did not show any rise in temperature at all above normal. The fever gradually dropped and after May 12, no more fever was observed. His clinical improvement was marked: there was no more malaise, the appetite almost became voracious, he no longer felt droopy and had no more chilly sensations. His strength seemed to return so rapidly that he was soon asking permission to return to work. On reëntering the French Hospital he weighed 132 pounds, and on July 1 his weight was 138½ pounds. At this time he said he had never had any more trouble.

Summary. The 3 cases herein reported have continued to be observed from time to time. Each is well, has picked up weight, feels fine and is back at his work. In each instance it appeared that the administration of acriflavine was followed by a definite clinical improvement in the patient's condition. In the first case the fever likewise seemed to decline very definitely, following the use of this drug; whereas, the other 2 cases—although showing a definite tendency to a lessened fever—did not appear to be as definitely affected in this respect. The latter cases, however, were chronic in type when seen by me. Each sought relief from a recrudescent attack; and the third one was the most protracted case, resistant to several forms of therapy and very stubborn to every form of treatment, including the first series of acriflavine administrations. In this third case the disease had become deep seated and very probably involved many of the hidden lymph nodes. Because of this probable extensive involvement of the lymphatic system, the illness was protracted and stubborn in its response to all the forms of therapy used.

In no case was any disagreeable reaction observed from the use of acriflavine. Actually, aside from an occasional slight rise of temperature, following the administration of this drug, no untoward response was at any time seen. The writer feels that—if the drug was actually of any benefit—it probably acted as a bacteriostat. As such, the acriflavine very probably inhibited the growth of the organisms sufficiently to permit the host enough time to increase his antibodies to the point of finally overcoming the infection. In each case, it appears that the body defense did not become definitely

tions of space do not permit of a complete résumé, but there is adequate convincing evidence that the local application of sulfonamide compounds in tissue is an effective bacteriostatic agent.

Vehicle of Application. Application of sulfonamides to the skin by dusting the powdered drug on the affected site has definite disadvantages in dermatologic therapy. The powder does not remain in contact with the site of infection unless an occlusive dressing is applied, and is easily washed away by serous or purulent secretion. It tends to become conglomerate and not to remain evenly distributed over the area of application. An effective vehicle should, we believe, accomplish the following: 1, retain the sulfonamide in a finely divided state at the site of application for a reasonable period; 2, permit close contact of the compound with the site of infection; 3, be miscible with serous and purulent drainage; 4, not form an impermeable and inert covering under which bacteria might grow readily; and 5, permit easy removal of bacteria contained in crusts and surface débris. In previous studies we have attempted to determine the best vehicle of application for certain of the commonly used skin antiseptics,¹² and have observed the effect of various ointment bases and antiseptics on the bacterial flora of the normal skin.¹⁶ Applying the criteria listed above to various ointment bases in common use, it seems to us that most of them have certain disadvantages. The all-grease bases, such as petrolatum, lanolin, or simple ointment are effective in retaining a medicament at the site of application, but may not allow intimate contact of the antiseptic agent with the site of infection, do not mix easily with exudate, are sometimes removed with difficulty, and probably increase the growth of bacteria under the grease film. Substances such as pectin, tragacanth, and bentonite are useful, but dry and flake off quickly unless a considerable amount of an anti-drying agent is added. Lotions have a limited usefulness. On theoretical grounds, water-in-oil emulsions may not show any superiority over grease bases, especially if the active ingredient is contained in the external oil phase. An oil-in-water emulsion type base, in which the sulfonamide is first suspended or dissolved in the external aqueous phase, offers certain advantages in that it theoretically allows evenly distributed contact of the antiseptic with the site of infection, has a low surface tension, mixes readily with exudates, and is easily removed by washing.

Of the available sulfonamides we have employed all of the following to some extent, sulfanilamide, sodium sulfadiazine, and sulfathiazole. However, the bulk of our experience has been with sulfathiazole. It has the advantage of being relatively effective against both staphylococci and streptococci. It is little soluble, and the probability of significant absorption is not great. The sodium salts of the various sulfonamides have a possible advantage of greater

many minor dermatologic conditions the risk of reactions following the administration of sulfonamides by mouth is unjustified, and the present methods of local treatment of superficial skin infections are not entirely satisfactory.

This study is an attempt to determine: 1, the effectiveness of local sulfathiazole therapy in the treatment of various dermatologic lesions caused in whole or in part by pyococci; 2, the most efficient vehicle of application; 3, the evidences of local or general toxicity incident to such therapy; and 4, the effect on the various bacteria found in such lesions. A total of 190 patients has been treated.

The recorded studies concerning the local application of sulfonamide compounds in superficial dermatologic infections are as yet few in number, and some of them do not include detailed data. Jaeger⁷ first applied Prontosil to various dermatoses in a vehicle of equal parts of acetone and alcohol, and in cholesterinized petrolatum. He noted no irritation at the site of application, and reported good results in infectious skin diseases, sweat gland abscesses, dermatomycoses, infected wounds, lupus vulgaris, and burns. Occasional improvement was noted in cases of eczema. Merz¹⁴ used 10% sulfanilamide ointment in acne, furunculosis, and impetigo, occasionally combining it with oral or intramuscular administration. Lamers¹¹ treated herpes zoster with an acetone-alcohol tincture of Prontosil, with "invariably good results." Other studies include those of Dey,² in which he applied sulfanilamide powder in 20 cases of boils, ulcers, and other mild skin infections, and Smith,¹⁸ in which 5 cases of infected ulcers and burns were treated by soluble Prontosil in compresses or lanolin ointment.

Veal and Klepser²⁰ treated 140 patients suffering from pyogenically infected wounds, with sulfanilamide powder and an ointment containing 10% sulfanilamide, 2% allantoin, and 0.5% chlorbutanol in a glycerinated stearic acid ointment. They noted early inhibition of bacterial growth, with sterilization of the wound in about 8 days. It was found that the ointment form seemed to promote granulation tissue, and initial application of the powder for from 4 to 6 days, followed by use of the ointment, was suggested. Guyton⁵ found that the use of sulfanilamide in ointment had no striking effect attributable to sulfanilamide alone in catarrhal or gonorrheal conjunctivitis, or in trachoma. The results in corneal ulcers were good. Solutions of sulfanilamide were found to be less effective than ointments, and the details of preparation of a suitable base are given. The base employed was apparently of a water-in-oil emulsion type. The sodium salt of sulfapyridine was found to be irritating, apparently because of its higher pH.

The most extensive studies of local sulfonamide therapy have been concerned with its use in surgical conditions, particularly infected wounds,⁶ after clean operative surgery,⁹ and in compound fractures.⁸ The references given are representative, since restric-

injury. At times the secondary infection was acute and overt, with pustules, erythema, pain, lymphangitis, and occasional evidence of general reaction. This was particularly true in dermatitis venenata or fungous

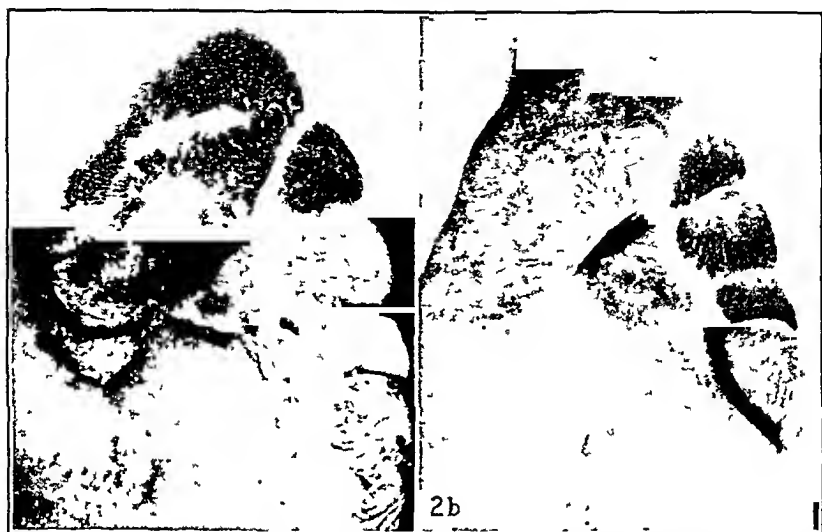


FIG. 2.—*a*, Intertriginous inflammatory eczema of toes suggesting a superficial fungous infection. No fungi were found on repeated culture, hemolytic streptococci isolated in pure culture. *b*, After 1 week of treatment with sulfathiazole emulsion ointment. In this patient one foot remained clear and the other showed a recurrence which was not controlled by sulfathiazole ointment.

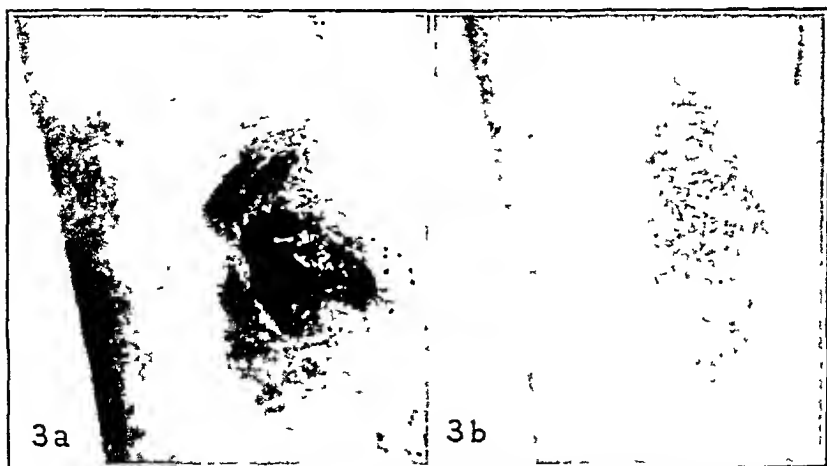


FIG. 3.—*a*, Chronic ulcer of calf of leg. Hemolytic streptococci isolated in pure culture. *b*, After treatment for 1 week with sulfathiazole emulsion ointment.

infections of the feet infected with streptococci. In secondarily infected eczema or seborrheic dermatitis, however, there may be little evidence of a local purulent reaction, and yet apparently pathogenic microorganisms may

solubility, but have a relatively high pH and may be more irritating when applied locally.

One hundred and ninety patients with various dermatoses have been treated with sulfathiazole applied locally in ointment form. Of these, in 134 it seemed probable that pyococci were solely or partially responsible for the eruption noted. It has been found convenient to divide these cases into the following groups, especially since the dermatologic terms applied to various superficial and deep pyodermas are numerous, confusing and often meaningless.

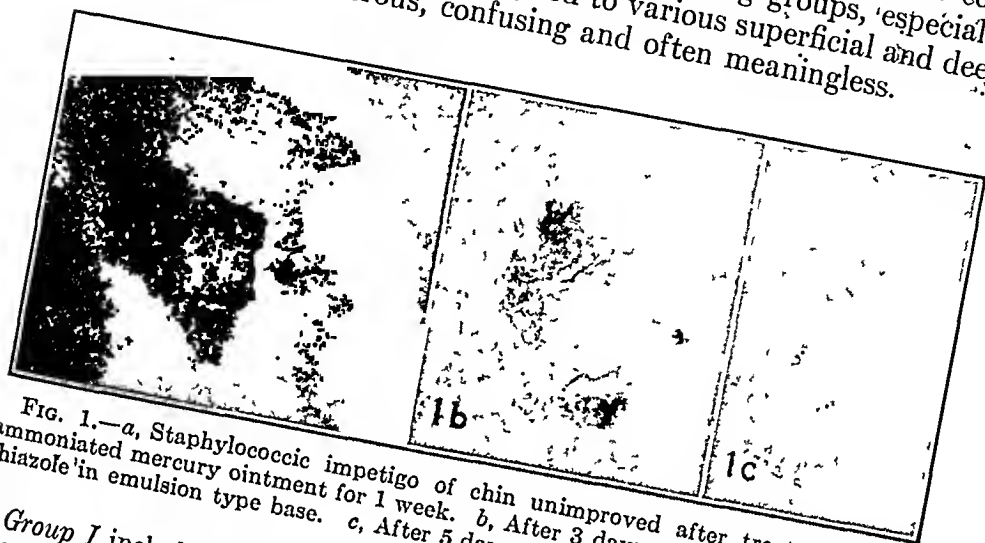


FIG. 1.—*a*, Staphylococcal impetigo of chin unimproved after treatment with ammoniated mercury ointment for 1 week. *b*, After 3 days of treatment with sulfathiazole in emulsion type base. *c*, After 5 days of treatment.

Group I includes all cases in which a pyogenic infection was apparently the primary cause of the skin changes. These were all acute cases of from a few days to 1 month in duration and included streptococcal and staphylococcal impetigo, infectious eczematoid dermatitis, Bockhardt's follicular impetigo, and superficial ecthyma. The lesions were superficial in character, not ordinarily followed by scarring, and characterized by pustules and seropurulent crusts (Fig. 1 A-C).

Group II includes cases of chronic eczematoid dermatitis in which pyogenic infection was at least a partial etiologic factor. Often there were no frank discrete pustules, but simply diffuse erythema, scaling, maceration, and fissures. These conditions are frequently diagnosed on morphologic grounds as fungous or *Monilia* infections. Included are acute intertrigo (behind ears, under breasts, in crural folds, gluteal cleft, and between toes), dermatitis repens, chronic infectious eczematoid dermatitis, and coccigenous sycosis. They are characterized by frequent contributory general medical or local factors, including obesity, diabetes, local vasomotor changes, hypersensitivity to bacterial or fungous antigens, and hyperhidrosis (Fig. 2 A, B).

Group III includes chronic deep ulcers apparently caused by pyococci. Such lesions are caused by a variety of microorganisms, produce varying degrees of scarring, and are also frequently associated with important contributory local or general factors, including vascular disturbances, trauma, anemia, and diabetes. In this series we did not encounter a case which we felt corresponded to the chronic symbiotic infections described by Meleney¹³ or the phagedenic ulcers recently discussed by Greenbaum¹ (Fig. 3 A, B).

Group IV includes acute or chronic pyoderma secondary to eczema, fungous infections, dermatitis venenata, seborrheic dermatitis, herpes or

By 100% improvement is meant a rapid and complete return of the skin to its normal state. The rapidity of response to local-sulfathiazole therapy, when it is to prove effective, surpasses that seen with any other local antiseptic, in our experience. Cases classified as showing 75% improvement responded rapidly to local sulfathiazole therapy, with relief of symptoms, but did not progress to com-

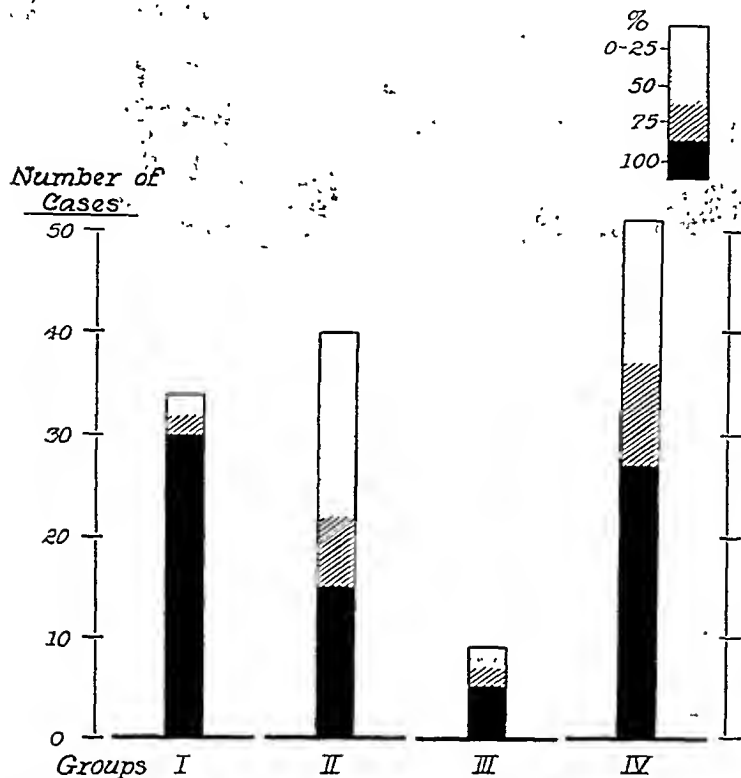


FIG. 5.—Results of local sulfathiazole therapy in various types of superficial dermatoses associated with infection.

Group I—Primary pyoderma (impetigo, acute infectious eczematoid dermatitis, and so on).

Group II—Chronic eczematoid and intertriginous lesions of varied etiology, including pyogenic infection.

Group III—Deep chronic ulcers of skin and subcutaneous tissues.

Group IV—Secondary pyogenic infections of preëxistent dermatoses (including dermatitis venenata, fungous infections, and eczema).

plete cure, and other measures became necessary. A 50% improvement indicates definite lessening of objective and subjective signs and symptoms of infections, and could be classed as "satisfactory." Improvement under 50% was partial and often temporary and could be duplicated or surpassed by a number of other local methods of treatment.

It is noted that in primary superficial pyodermias, rapid, complete cure was obtained in 30 of 35 cases treated. In such cases the

be repeatedly recovered over a long period of observation. In our experience, acute flare-ups of ringworm of the feet are more often due to pyogenic invaders than to the fungi themselves.



FIG. 4.—*a*, Acute streptococcal pyoderma complicating chronic intertriginous fungous infection of toes. Associated femoral adenopathy. *b*, After treatment for 2 days with sulfathiazole emulsion type ointment. The chronic underlying fungous infection was not affected.

In addition we have treated 30 patients suffering from various miscellaneous dermatoses, including dermatitis and eczema, dermatophytids and "pyids," cellulitis and erythema multiforme. In some of these, occasional good results follow sulfonamide therapy by mouth. Nine patients with folliculitis or furunculosis were treated, and 13 patients with acne.

The types of bases used in this study were as follows:

Grease base:

Sulfathiazole	5.0%
Simple ointment (U.S.P.)	95.0%

"Vanishing" type stearate base:

Sulfathiazole	5.0%
Carbitol	10.0%
Stearic acid	20.0%
Peanut oil	4.0%
Potassium hydroxide	1.0%
Water*	60.0%

Pectin base:

Sulfathiazole	5.0%
Pectin	10.0%
Benzoic acid	0.2%
Ringer's solution*	84.8%

Oil-in-water emulsion type base:

Sulfathiazole	5.0%
Sodium lauryl sulphate	1.0%
Stearyl alcohol	10.0%
Cetyl alcohol	3.0%
Spermaceti	10.0%
Glycerine	10.0%
Water*	61.0%

* Glycerine may be added for its anti-drying action without impairing the action of sulfathiazole. Dr. R. H. Blythe prepared the ointments used in this study.

Clinical Results. In Figure 5 are given the results of treatment in 134 patients with dermatoses due in whole or in part to pyococci.

so variable that any conclusions must await experience in a large number of cases. It was noted that the emulsion or stearate vanishing bases did not cause flare-ups of acne of the type sometimes noted after application of various greases.

Directions for Application of Ointment. In order that an adequate concentration of sulfathiazole may be maintained at the site of infection, and that the effect of substances interfering with its action (peptone, pus) may be counteracted, certain rules for application have been established. These are:

1. Application of the ointment four to six times daily, unless a closed dressing is used.

2. Careful cleansing of the affected area as vigorously as may be tolerated by the patient. Crusts and débris from vesicles and scales should be removed scrupulously. Saline, boric acid, or dilute potassium permanganate solution applied as compresses or soaks are useful in cleaning up lesions.*

3. Surgical drainage of all pustules or vesicles, even the smallest. *Sulfathiazole ointment has little effect when applied to the top of an intact pustule.* Patients or attendants may be trained to open pustules with clean manicure scissors safely and satisfactorily.

Bacterial Findings. In 119 of the 134 cases in Groups I, II, III and IV, of this series, bacterial cultures were performed. The technique will not be given in detail. It is important that cultures be incubated under both aerobic and anaerobic conditions.

It is often difficult to evaluate the significance of a particular strain of bacteria isolated from a lesion of the skin, particularly in chronic intertriginous or patchy eczematoid lesions. We record these bacterial findings as factual information, but shall not in this paper attempt an extensive review of the controversial opinions as to the pathogenicity of the organisms recovered. Since the original work of Sabouraud¹⁷ on streptococcic dermatoses, several studies of the rôle of streptococci in various skin lesions have appeared, of which those of Mitchell,¹⁸ Kinnear,¹⁹ and Epstein³ are representative examples. In several thousand scrubs of the normal skin of the hands and forearms of 8 subjects, using the Price technique, we have not encountered a single culture of streptococcus hemolyticus. This is not in accord with the statements of other observers.²¹ The rôle of staphylococci in a particular skin lesion is even more difficult to determine, because they are regularly isolable from normal skin. We believe that some of the findings in cases in which bacterial cultures were done repeatedly during sulfathiazole therapy may shed light on the significance of the organisms recovered.

Figure 6 gives the bacterial findings in our cases, together with the corresponding number of cases showing a "satisfactory" improvement of over 50% of sulfathiazole therapy. The patients grouped under "streptococcus" or "staphylococcus" showed a pure

* Sulfathiazole in an emulsion type base may be used in place of soap. A study of its effect in reducing the bacterial flora of the normal skin is in progress.

changes were easily determinable in 48 hours, often in 24. Streptococcic impetigo responded most rapidly, with absolute prevention of new lesions as a rule, and complete disappearance of all lesions in 4 to 5 days.

In the group of processes of chronic infectious eczematoid character (Group II), the results were less striking, 15 of the 40 cases showing a rapid and complete cure, 7 a 75% improvement, and 8 a 50% improvement. Nevertheless, because these cases are ordinarily very resistant to other methods of treatment in our experience, local sulfathiazole is regarded as being of distinct value.

In 9 cases of relatively deep chronic ulcers of the skin and subcutaneous tissues, complete rapid healing was noted in 5 (Fig. 3 A, B). In such cases it was ordinarily convenient to pack the ulcer with sulfathiazole emulsion and apply a dressing.

In Group IV, in which the infection was obviously a complication of a preëxistent dermatosis of chronic or acute character, complete cure, with return of the skin to a normal state within 1 week, was noted in 27 of 51 patients. No irritation from the sulfathiazole ointment was noted in patients suffering from a previous dermatitis venenata. There was no indication that sulfathiazole ointment had any effect on an underlying chronic fungous infection or seborrheic dermatitis, and only occasionally did a preëxistent eczema show permanent improvement.

An illustrative case in this group is the following:

CASE 1.—J. R., a white girl, aged 9, sustained a dermatitis venenata due to rhus, on the legs, arms, and face. Five days after the dermatitis appeared, thin-walled superficial pustules on a highly inflammatory base were noted (typical of streptococcic pyoderma). These increased in extent, affecting principally the previously dermatitic skin. Femoral, axillary, and cervical lymphadenopathy appeared, and the fever rose to 104°. A pure culture of hemolytic streptococci was obtained. The pustules were all opened, tissue debris and crusts removed, and sulfathiazole emulsion ointment applied every 3 hours. The temperature became normal in 24 hours, and remained so. Complete healing occurred within 4 days. In another patient with an entirely similar eruption, sulfathiazole was also given by mouth, with similar prompt improvement.

In the miscellaneous group of 30 cases of dermatitis, eczema, "ids," low-grade cellulitis, and erythema multiforme, no improvement was noted in 17, and the moderate improvement noted in the remaining 13 cases was no more than would have been expected from application of a bland ointment, or incidental to the normal course of the disease.

Our experience with deep follicular infections, either primary or secondary to acne vulgaris, is as yet limited. It is believed that sulfathiazole ointment has no effect on a developing unopened lesion. After surgical drainage, it is uncertain that improvement is more rapid with sulfathiazole ointment, but we have the impression that the development of secondary satellite lesions is impeded. The course of folliculitis, furunculosis and pustular acne vulgaris is

isms, complete cure was obtained in 12 of 28 cases. When the culture revealed principally staphylococci, complete cure was noted in only 4 of 26 patients, and 10 were unimproved. These results might be interpreted in two ways, either sulfathiazole ointment is less effective against infectious skin lesions in which large numbers of staphylococci are found, or dermatoses associated with local staphylococcic infection are more readily influenced by standard treatment measures and sulfathiazole ointment offers less superiority.

*Results in Cases of Superficial Infection
Previously Resistant to
Other Types of Treatment*

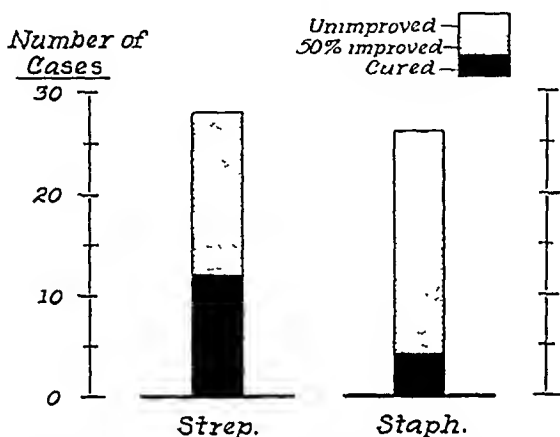


FIG. 7.—Local sulfathiazole therapy in patients previously resistant to various other types of treatment.

Comparative Effect of Various Bases. In our initial experience with all-grease bases, it was soon apparent that the clinical effect, while often surpassing the improvement obtained with ammoniated mercury ointment, was not as good as when the sulfathiazole was incorporated in an emulsion or stearate vanishing type base. After treatment of approximately 15 cases, all-grease bases were therefore discarded for a time, and our studies confined to the vanishing or emulsion type bases. More recently we have compared the effect of sulfathiazole in emulsion base and in a proprietary grease base apparently containing a mixture of petrolatum and lanolin. We have concluded that an all-grease vehicle for the application of sulfathiazole, while occasionally moderately effective in superficial pyodermas, has a slow and inefficient action when compared with either an emulsion or stearate type base. The following case is illustrative:

CASE 2.—R. B., a white male, aged 5, presented a widespread severe pyoderma with superficial pustular, bullous, and ecthymatous lesions distributed on the scalp, face, back, arms, and thighs. The initial lesion had been noted on the face 1 week previously, and the extension to other parts of the body had been rapid, with chills and fever for 2 days. Ammoniated

or heavily predominant culture of the corresponding bacterium, always of hemolytic type. Under "mixed" infections are grouped those cases in which a large number of strains were obtained, without one clearly predominating. The strains included *Strep. viridans*, indifferent streptococci (short chain, non-hemolytic), *Staph. aureus* and *albus*, micrococci, *sarcina lutea*, and diphtheroids. It will be noted that when hemolytic streptococci were recovered as the predominant organism, some clinical improvement was always noted following sulfathiazole therapy. In cases in which hemolytic

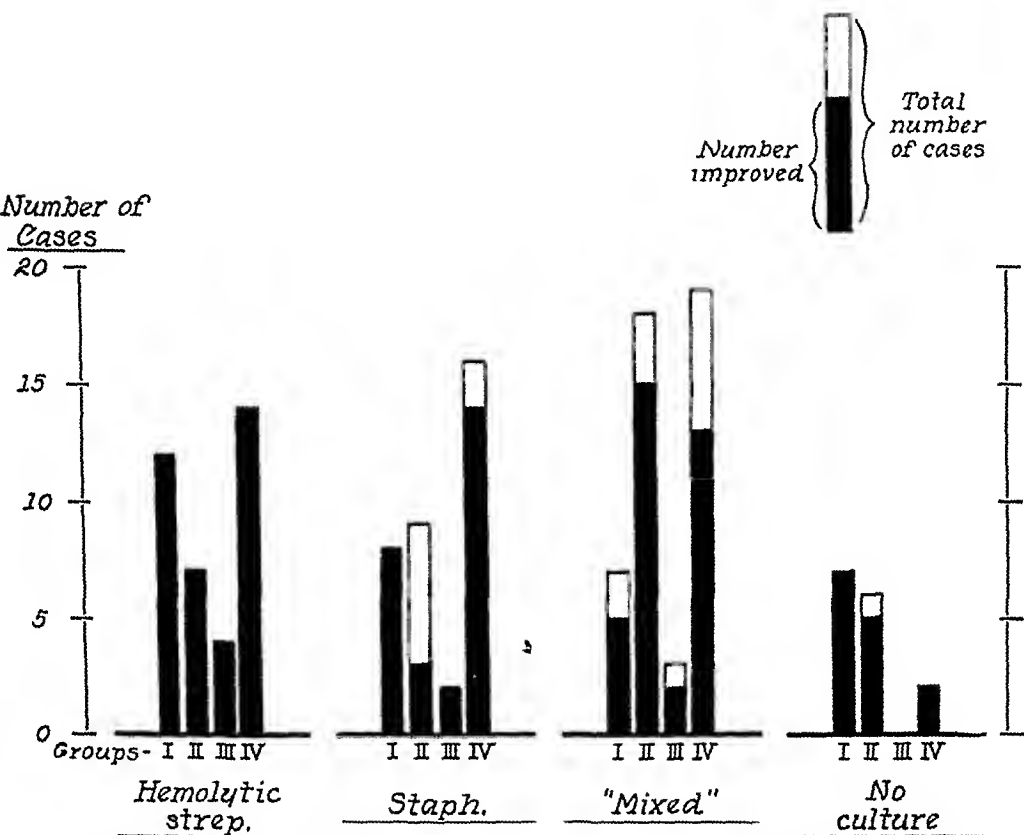


FIG. 6.—Results of bacteriologic culture in 119 cases. (The number of cases showing a satisfactory improvement of over 50% is indicated in black.)

staphylococci were recovered in pure or predominant culture, the clinical results were less striking, particularly in the group of chronic eczematoid dermatoses with evidence of infection. In the cases showing "mixed" cultures the results were likewise not as good as when streptococci were predominant.

The findings in the cases previously resistant to other types of therapy seem instructive (Fig. 7). These were principally patients with dermatoses of Groups II, III or IV, and the prolonged previous treatment included variously potassium permanganate soaks, ammoniated mercury ointment, Castellani's carbolfuchsin paint, gentian violet, acriflavine and Roentgen ray therapy. In such patients, when hemolytic streptococci were the sole or predominant organ-

Absorption of Sulfathiazole, Local and General Evidence of Toxicity.

In most of the patients in whom a sulfathiazole ointment was used, the total amount of sulfathiazole applied to the skin was so small as to make the possibility of absorption of significant amounts unlikely. For instance, in the usual case of impetigo, not more than 30 gm. of the ointment were required daily, a total of 1.5 gm. of sulfathiazole. The largest amount required was in a patient with a generalized dermatitis from which hemolytic streptococci were repeatedly isolated, when 120 gm. of the ointment were required daily, a total of 6 gm. of sulfathiazole. In no patient were there any symptoms or signs indicative of sulfathiazole toxicity. In 40 patients under treatment with varying amounts of sulfathiazole ointment, determination of the blood sulfathiazole level was done according to the method of Sunderman and D. S. Pepper.¹⁹ In no patient was any sulfathiazole detectable in the blood.* In 4 patients experimental introduction of sulfathiazole through the skin was attempted by the application of 180 gm. of the emulsion daily (9 gm. sulfathiazole). In 1 of these patients, in whom there were very large areas of dermatitis, a "barely detectable" trace of sulfathiazole (under 0.05 mg. per 100 cc.) was found in 2 of 12 determinations performed; in the rest no sulfathiazole was detectable.†

We have seen no indication that sulfathiazole ointment applied to one area of the body has any effect on lesions at another site, *i. e.*, that applied sulfathiazole acts by absorption into the blood stream. Its effects are purely local, at least in superficial dermatologic lesions. In interpreting this finding it should be kept in mind that there are included no patients in whom very large ulcers were packed with considerable amounts of sulfathiazole ointment. Under such conditions some absorption of sulfathiazole might be expected, but probably of an order less than would be the case with more soluble sulfonamide compounds. In our experience with superficial dermatologic lesions, local sulfathiazole therapy applied in all-grease, stearate or emulsion ointments is entirely free from any general reaction attributable to the sulfathiazole.

In a few patients with chronic eczematoid eruptions, flare-ups have been noted in conjunction with the use of sulfathiazole ointment, particularly when the stearate type base was used. In no patient was there any indication that the sulfathiazole *per se* was responsible, and no exacerbation was noted in a patient with a dermatosis primarily due to infection. The emulsion and stearate bases contain certain possible contact sensitizing agents, including particularly sodium lauryl sulphate and glycerine, but a considerable previous experience of two of us (D. M. P. and C. S. L.) with the various ingredients of these bases had not indicated that their sensitizing capacity is significantly high. Ordinary ammoniated mercury ointment, even in strengths of 1%, has a far higher sensitizing

* The blood sulfathiazole determinations were done by Dr. F. W. Sunderman.

† This portion of the study was carried out by Dr. Elizabeth R. Constant.

mercury ointment had been applied for 2 days prior to admission, without effect. Between July 9 and 16, 1941, a 5% ointment of sulfathiazole in petrolatum and anhydrous lanolin was applied three times daily. Slight improvement occurred, though new lesions developed. Treatment was then changed to 5% sulfathiazole in an emulsion type base, and complete healing of all lesions occurred in 2 days.

In general, stearate "vanishing" bases have produced a more satisfactory effect than did various grease bases. At times, improvement following application of this type of base was as rapid as with the emulsion base. However, two disadvantageous features were noted, one being that the vanishing ointment tended to dry more rapidly, and the other that patients frequently complained that the stearate base was less soothing.

Our experience with the pectin type base is limited. We detected no advantage therapeutically, and such an ointment tended to flake off rapidly.

In summarizing the effectiveness of the various bases as a means of producing a satisfactory therapeutic action of sulfathiazole on superficial dermatologic infections, the following rather arbitrary method of expression might be used. If the emulsion type base is regarded as, say, 90% efficient, we would place the effectiveness of the stearate type base at approximately 70%, and the grease base as 50% or less. These are pure estimates, rapidity of action on the infection being the first criterion, but with consideration of other factors such as the frequency of application necessary, the subjective sensations of the patient following its use, washability, and apparent penetration under crusts and débris to the site of infection.

Bacteriologic Findings in Treated Patients. In patients in whom the skin lesions did not heal within a few days, bacteriologic culture was done at weekly intervals. When large numbers of indifferent streptococci or *Strep. viridans* were found (11 cases), disappearance of these bacteria was noted within 2 weeks. In 23 cases in which hemolytic streptococci were predominant, in only 1 did the streptococci persist in hemolytic form. In 8 cases the streptococci disappeared entirely within 2 weeks. In 9 cases the organisms became indifferent (non-hemolytic, short chain) within 2 weeks, and disappeared entirely within 1 month. In the rest of these cases the streptococci became indifferent in varying periods of time and then disappeared, with the exception of the above noted case. In chronic eczematoid lesions, disappearance of streptococci was not always accompanied by clinical improvement. Hemolytic *Staph. aureus* persisted apparently unchanged in 90% of patients in whom it was the predominant organism recovered. In a few cases the staphylococci were apparently replaced by micrococci.

In general, *Strep. hemolyticus* tended to become indifferent in type and then disappear in lesions treated with sulfathiazole ointment. *Strep. viridans* and indifferent streptococci tended to disappear promptly. *Staph. aureus hemolyticus* tended to persist in treated lesions, regardless of the clinical course of the process.

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THE CAUSATIVE RELATIONSHIP OF DERMATOPHYTOSIS TO THROMBOANGIITIS OBLITERANS.

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THE cause of thromboangiitis obliterans is unknown. Ergot,¹⁰ tobacco,⁸ typhus,⁷ streptococci,¹⁶ and hormonal disturbances¹² have been proposed as etiologic agents but have not been accepted, as they could not adequately explain the entire syndrome.

In this Peripheral Vascular Clinic, studies in thromboangiitis obliterans revealing a higher incidence of dermatophytosis and a more frequent reaction to trichophytin than in controls were followed in 1939 by the observation of patients with thromboangiitis obliterans in whom acute dermatophytosis immediately preceded attacks of acute migratory phlebitis.

Dermatophytosis is present in many patients with peripheral arterial disease, but it has always been looked upon merely as a complication which must be treated to avoid ulceration and gangrene. As the possibility was kept in mind that dermatophytosis might stand in causative relationship to thromboangiitis obliterans, certain clinical features of thromboangiitis obliterans appeared to be clarified which could not otherwise be explained. Such is the relapsing nature of thromboangiitis obliterans; the limitation of the lesions, in 95% of patients with thromboangiitis obliterans, to the blood-vessels of the legs and arms and the distorted toe nails which

capacity on the skin that any of the substances used in these studies.

In resistant dermatoses, local sulfathiazole therapy has been combined with other types of therapy, including ammoniated mercury ointment, carbol-fuchsin paint, tar ointment, Roentgen ray and ultraviolet therapy, acriflavine and potassium permanganate compresses, and quinolor ointment. There was no indication of incompatibility insofar as the therapeutic results were concerned. We have treated a few patients recently with an ointment containing 5% of sulfathiazole and of sulfanilamide, with no evidence of incompatibility, but also without demonstrating any marked advantage in such a combination.

Conclusions. 1. Sulfathiazole in an oil-in-water emulsion vehicle is effective in the treatment of primary superficial infections of the skin, including staphylococcic or streptococcic impetigo, infectious eczematoid dermatitis, Bockhardt's follicular impetigo, and superficial ecthyma.

2. It is equally effective in acute secondary infection of various preëxistent dermatoses, including particularly pyogenic complications of fungous infections and of dermatitis venenata.

3. Certain criteria for the effective local application of sulfathiazole have been established, and an oil-in-water emulsion vehicle, in which the sulfathiazole is suspended in the external aqueous phase, has apparently met these requirements satisfactorily. A vanishing type stearate base was somewhat less effective than the emulsion type base. Grease bases proved definitely inefficient.

4. Sulfathiazole ointment is useful in chronic deep ulcers of the skin and subcutaneous tissues.

5. In various chronic eczematoid lesions, from which large numbers of staphylococci or streptococci may be recovered, the effects of sulfathiazole ointment are much less striking than in impetigo, but such treatment is occasionally very helpful.

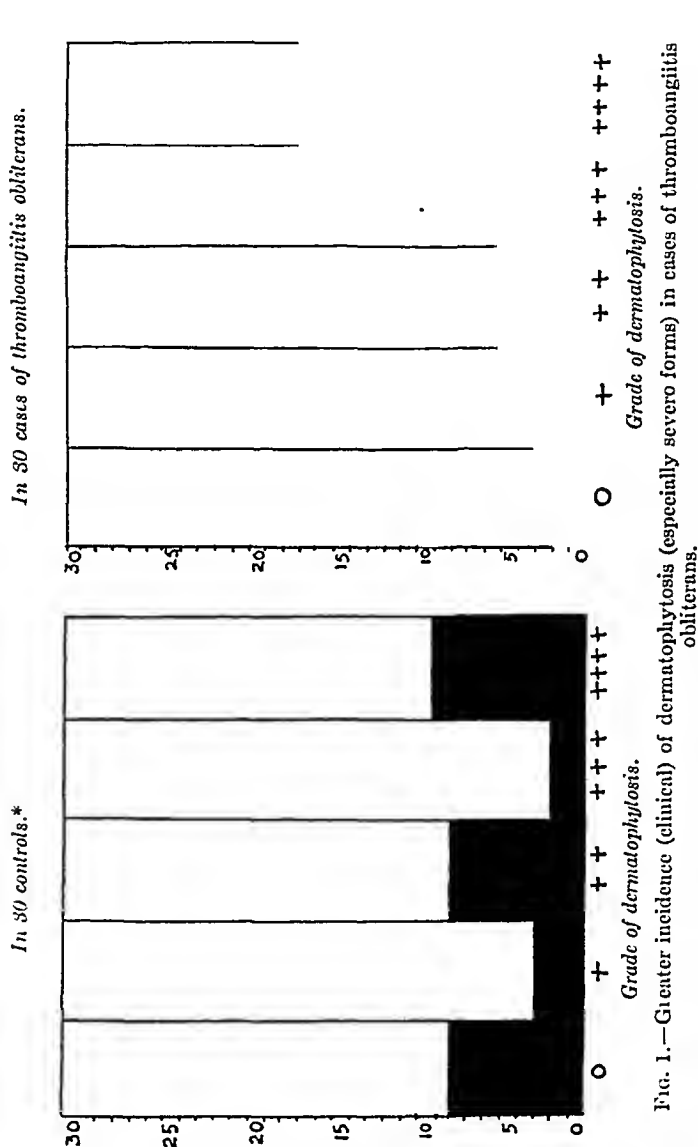
6. There was no evidence of absorption of sulfathiazole in the patients treated, and no local or general toxic reactions.

7. Superficial infections from which streptococci were recovered responded somewhat more rapidly and completely than those yielding staphylococci on culture.

Since this paper was written we have encountered one instance of cutaneous sensitivity to sulfathiazole. In a recent paper, Keeney *et al.** report good results in 60 patients with cutaneous infections treated with 5% sulfathiazole in a base containing equal parts of hydrous wool fat and vanishing cream. In 6 of 8 eczematous infants in which sulfathiazole ointment (amount not stated) was applied to one-half of the body, they found sulfathiazole to be detectable in the blood in concentrations of from 2 to 3.5 mg. per 100 cc. They observed no absorption in adults. In a study of sulfathiazole absorption through the skin of infants and children, now in progress, Jaquette and one of us (D. M. P.) have been unable to demonstrate significant blood levels of sulfathiazole in 10 normal infants weighing from 7½ to 26 pounds following application of 30 gm. of sulfathiazole ointment daily, and in 5 children weighing between 26 and 41 pounds, following application of 60 gm. of ointment (3 gm. sulfathiazole).

* Keeney, E. L., Pembroke, R. H., Chatard, F. E., and Ziegler, J. M.: J. Am. Med. Assn., 117, 1415, 1941.

microscopically, upon injection of 0.1 cc. trichophytin into the left forearm, developed erythema and induration of most of the forearm within 48 hours, with a vesicle 2 cm. in diameter at the site of injection.



Migratory Phlebitis and Dermatophytosis. Ten of the patients were observed during attacks of migratory phlebitis, characteristic acute lesion of thromboangiitis obliterans. Seven of these had an exacerbation of dermatophytosis preceding the attack of phlebitis,

were formerly attributed to ischemia, but which yield fungi on culture.

It should be emphasized that fungi are the one group of pathogenic organisms which are present in the same regions involved by thromboangiitis obliterans and that no investigation has been made as to whether they could or could not produce this vascular disease. As little is known of the relation of fungous diseases to other processes and with clinical observations suggesting that the migratory phlebitis and arteritis in some patients with thromboangiitis obliterans is preceded by a flare-up of dermatophytosis, it was thought worth while to investigate the possibility of this causative relationship. With the exception of a report by Thompson,¹⁷ who also believes in this theory, nothing has been published on this subject.

Dissemination through the blood stream of dermatophytosis, an infection of the skin by fungi such as *Trichophyton*, *Epidermophyton* or *Monilia*, frequently results in the production of secondary lesions which have been called "dermatophytids" or "moniliids." Evidence^{13,19} points to sensitization of the skin to the fungi or their products as a cause for these lesions.

Incidence of Dermatophytosis in Thromboangiitis Obliterans. Thirty patients with thromboangiitis obliterans were examined for evidence of dermatophytosis (Fig. 1). Twenty-eight (93%) had dermatophytosis clinically, severe in 20. Of 30 controls, men between the ages of 20 and 50 without thromboangiitis obliterans, 22 (73%) had dermatophytosis clinically, severe in 9. Vesicles, extensive scaling, fissures and involvement of nails were definitely more common among patients with thromboangiitis obliterans than among the controls. On microscopic examination fungi were found in 5 to 12 patients with thromboangiitis obliterans. This is the approximate proportion usually obtained in patients with dermatophytosis.

Skin Tests With Extracts of Fungi. The work of Lewis and Hopper¹¹ indicates that a positive trichophytin test is indicative of present or past infection by fungi. Skin tests were made with trichophytin* 1:30 in 30 patients with thromboangiitis obliterans. After 48 hours 24 patients (80%) were positive to trichophytin (see Fig. 2). The 2 patients with thromboangiitis obliterans who showed no evidence of dermatophytosis were positive to trichophytin. Of the 30 controls, men between the ages of 20 and 50, without thromboangiitis obliterans, 6 (20%) were positive to trichophytin. Of the 8 controls without clinical evidence of dermatophytosis, none gave a positive reaction to trichophytin. It can be seen from Figure 2 that there were four times as many patients with thromboangiitis obliterans who gave positive skin reactions than those without thromboangiitis obliterans. One patient (J. H.), with thromboangiitis obliterans with slight dermatophytosis, positive for fungus

* Fungus extract made from *Trichophyton interdigitale* (Lederle).

J. C., a man of 33, was seen in August, 1939, with a popliteal occlusion and dermatophytosis, the latter being too mild to warrant treatment. In October he returned with a history of severe itching between the toes which had developed 3 weeks previously. Two weeks after the appearance of the itching he noticed red, tender areas along the veins of the right leg. On examination he had a severe, moist type of dermatophytosis between the toes in the involved leg with five areas of acute migratory phlebitis. In the other leg, which had no arterial disease or phlebitis, the dermatophytosis was slight and dry. A skin test with trichophyton which had been done in August was strongly positive.

T. C., a man of 40, was seen first in 1936 with a history of having had dermatophytosis for years. In 1933 he began to have attacks of migratory phlebitis and developed intermittent claudication. He observed that the migratory phlebitis flared up whenever the dermatophytosis became severe. He made wooden shoes so that he could continue taking showers in the plant where he worked without making his dermatophytosis worse. This occurred before he was seen at the University Hospital in 1936. On examination he had occlusion of both popliteal and both ulnar arteries. From 1936 to 1939 he had no exacerbation of his dermatophytosis and no migratory phlebitis. In March, 1939, he developed migratory phlebitis on his hands and in August, 1939, in his right leg and right index finger. Microscopic examination of scrapings from his nails was positive for fungi.

B. T., a man of 56, had a history of thromboangiitis obliterans for the past 15 years. He had no pulses in either femoral artery. On examination in May, 1940, he had a quiet dermatophytosis between the toes and of the nails. In June, 1940, the dermatophytosis became acute and remained so for about a month. In July he came in with acute migratory phlebitis on the dorsum of the foot.

Similarity in the Locations of Inflammatory Lesions of Thromboangiitis Obliterans and Dermatophytosis. Since the fungi which cause dermatophytosis are found in the toes and feet and dermatophytids in the hands, it was thought important to study the location of migratory phlebitis and acute arteritis, the primary lesions of thromboangiitis obliterans (Fig. 3). In 42 patients with thromboangiitis obliterans, migratory phlebitis occurred 30 times in the foot and ankle, 12 in the leg, 5 in the thigh, 11 in the hand and wrist and 4 in the forearm. The frequency with which migratory phlebitis begins in the feet is worthy of comment as other forms of phlebitis occur more frequently in the legs and thighs. That acute arteritis of thromboangiitis obliterans seems to have a similar peripheral distribution at the onset of the disease is shown by the pathologic studies of Buerger.⁵ In a typical case the older process is found in the distal portion of the artery, the more recent inflammatory process being found at a higher level. It will be remembered, however, that thromboangiitis obliterans has been reported in parts of the body other than the extremities in about 5% of the patients.⁹ Systemic manifestations in dermatophytosis are rare but do occur (Pulvermacher,¹⁵ Bloch,² and Bruusgaard¹⁴).

In thromboangiitis obliterans and dermatophytosis the hands are often involved as well as the feet. In a group of 85 patients with thromboangiitis obliterans 40% with involvement of the feet had

and on examination all 7 had severe dermatophytosis. The possibility exists that ischemia may have predisposed to dermatophytosis, but there is no evidence to indicate that ischemia favors the development of the fungus disease. Furthermore dermatophytosis and

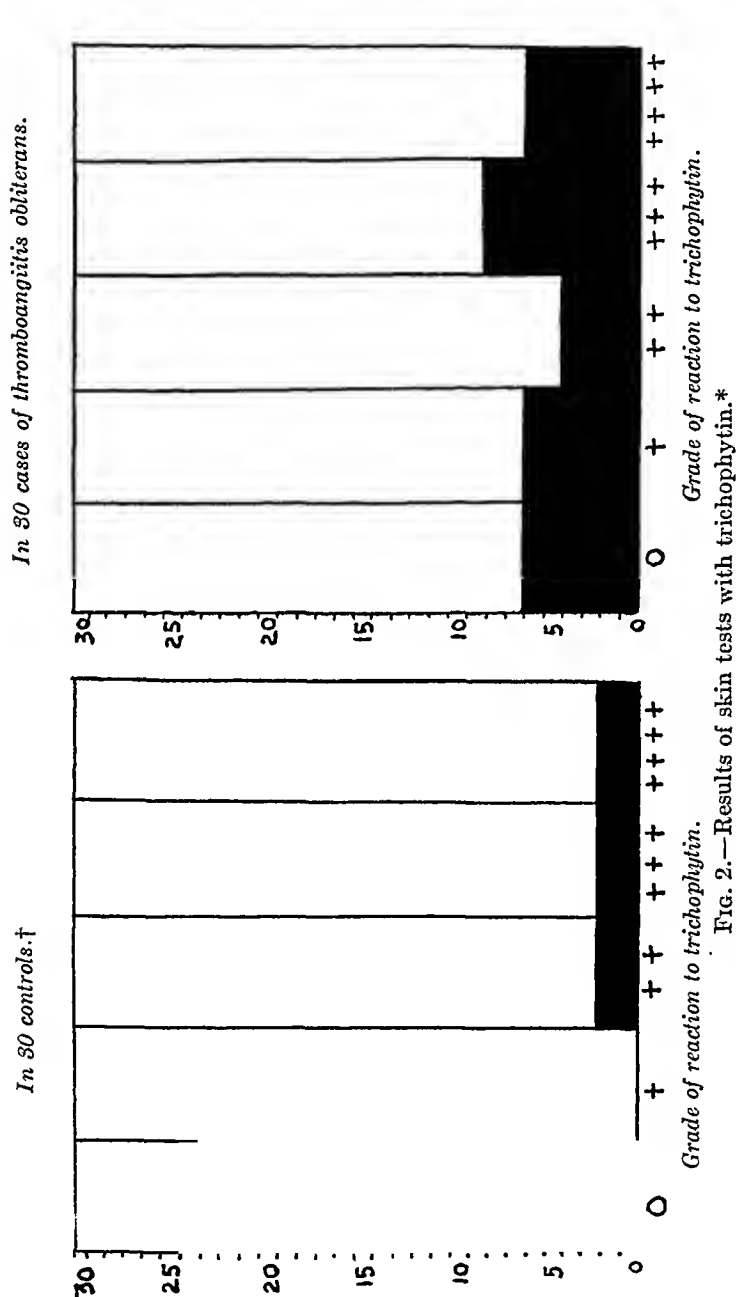


FIG. 2.—Results of skin tests with trichophyton.*

* Fungus extract made from *Trichophyton interdigitale* (Lederle).

† No thromboangiitis obliterans but same age (average 31) and sex (males, 29; females, 1) distribution as in cases of thromboangiitis obliterans.

migratory phlebitis are present in many patients before arterial occlusion and ischemia appear.

The time relationship between dermatophytosis and the appearance of migratory phlebitis is illustrated by the following cases:

Buerger,⁵ most of his patients with thromboangiitis obliterans came. Also, many dermatologists believe that following the war there was a great increase in dermatophytosis in this country. This, they attribute to the return of thousands of soldiers with ringworm infection. That this increase of dermatophytosis is more than can be



FIG. 4.—Fungous infection of toe nails in patient, male, age 42, with thromboangiitis obliterans. Culture of scrapings from nails positive for *Trichophyton gypsum*. Skin test with trichophytin positive (see Fig. 5).

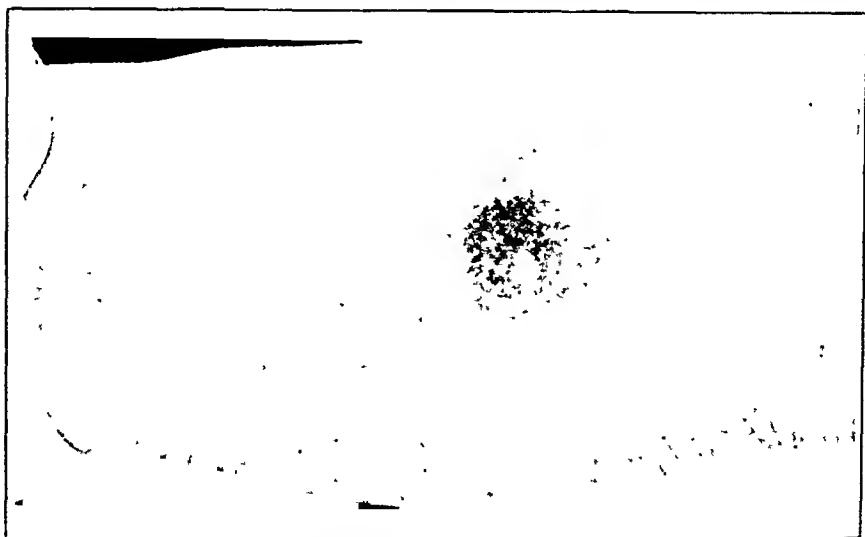


FIG. 5.—Positive skin test in same patient as in Figure 4.

the disease also in the upper extremities. Estimates of the percentage of dermatophytids of the hands in patients with acute dermatophytosis range from 3% by Shelmire⁶ to 50% by Loveman.⁶

Age Incidence. In both diseases the great majority of patients fall between the ages of 20 and 50 (White¹⁸ and Williams²⁰).

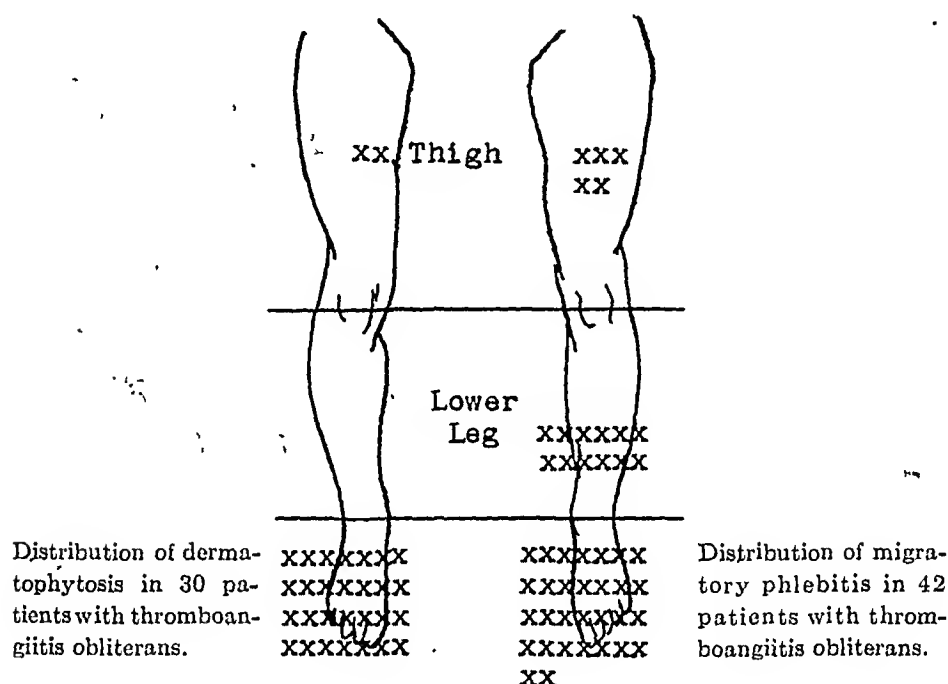


FIG. 3.

Relapse. The relapsing nature of thromboangiitis obliterans is well recognized and accounts for the progression of the disease in many patients. More than one attack of migratory phlebitis or arteritis occurs in almost all patients. Dermatophytosis likewise is a stubborn disease and repeated attacks are the rule. Complete cure is difficult and reinfection is common.

The Nails in Thromboangiitis Obliterans. Dystrophy of the nails is mentioned as characteristic of thromboangiitis obliterans (Buerger⁵ and Brown, Allen and Mahorner³). Examination of a number of patients with thromboangiitis obliterans with deformed, overgrown nails disclosed that these nails do not differ from similar nails seen in patients without vascular disease but with fungous disease of the nails. Cultures of fungi were obtained from the nails of the patient in Figure 4.

Epidemiology of Dermatophytosis and Increase in Incidence of Thromboangiitis Obliterans. In 1921 Anderson¹ reported that, between 1914 and 1921 the great majority of severe ringworm infections in immigrants occurred among those coming from the countries of southeastern Europe, the same region from which, according to

Comment. With the single exception of ergot, which is known to cause vascular disease, the rôle played by fungi in the possible production of thromboangiitis obliterans has never been explored. Ergot has been suggested as a possible cause of thromboangiitis obliterans, but few patients give a history of contact with ergot. On the other hand, most patients with thromboangiitis obliterans harbor the fungi which cause dermatophytosis. These fungi have never been regarded as etiologic or precipitating factors in thromboangiitis obliterans. Phlebitis has been attributed to dermatophytosis in a number of reports (Peck¹⁴ and Pulvermacher¹⁵). In 1 patient with generalized trichophytid,¹⁵ the phlebitis was thought to have had an allergic basis. In a review of fungous allergy, Peck¹⁴ gives a classification of trichophytids. Among these is a group which he designates "vascular trichophytids" which includes what he terms migrating phlebitis. It is reasonable to believe that in an occasional patient the blood-vessels may act as the "shock tissue" for a reaction to fungi. It is Thompson's¹⁷ belief also that vessels and other tissues may succumb to the products of fungi by means of an allergic reaction.

In seeking a possible relationship between dermatophytosis and thromboangiitis obliterans, one need not necessarily have the concept that the fungi are the sole cause of the vascular disease. It may be that fungi, being concentrated in the blood-vessels of the extremities, act on these vessels in such a manner that other agents such as tobacco or streptococci may bring on an inflammatory reaction. Another possibility is that fungi may precipitate or intensify an inflammatory reaction in blood-vessels previously acted upon by other agents such as tobacco or bacteria. It is not unlikely that more than one agent may cause the inflammatory reaction, which has been labeled thromboangiitis obliterans. The combination of the greater frequency of dermatophytosis with the more common use of tobacco in men, with the two factors acting to intensify each other, suggests an explanation for the greater frequency of thromboangiitis obliterans in men.

The prognosis in thromboangiitis obliterans has improved greatly in the past decade. During this period dermatophytosis in these patients has been treated as part of the usual therapeutic regimen because of the fear that the skin disease would open an avenue to infection and gangrene. The improved prognosis is, to be sure, due to many advances in our knowledge of thromboangiitis obliterans and its treatment. However, the incidental treatment of the dermatophytosis may well have been a factor.

Summary. A study has been made of patients with thromboangiitis obliterans with regard to the possibility that the disease may be caused or precipitated by fungi which cause dermatophytosis. While evidence has been presented suggesting an etiologic relationship between the two diseases, it is insufficient, at present, to be

accounted for by increased knowledge of the disease is suggested by White.¹⁸ Concurrently with this increased incidence of dermatophytosis there has apparently been an increase in thromboangiitis obliterans. At this hospital from 1910 to 1919 there were 18 patients with thromboangiitis obliterans, from 1920 to 1929 there were 32 patients and between 1930 and 1939 the number of patients had risen to 114.

Statistics indicate that dermatophytosis is as common among negroes as in the white race. The largest number of cases of thromboangiitis obliterans among negroes in the literature is the 5 reported by Yater,²¹ but why this disease is less frequently encountered in that race is not known.



FIG. 6.—Dermatophytosis between toes in patient, male, age 44, with thromboangiitis obliterans. Culture positive for fungus. Positive skin test with trichophytin.

Thromboangiitis obliterans occurs predominantly in men (97%). According to Lewis and Hopper¹¹ ringworm of the feet and hands is seen more frequently in males than in females. Yet many women have dermatophytosis and if fungi are the cause or precipitating factor in thromboangiitis obliterans, one would expect to find more female patients with the latter disease. A possible explanation of the apparent discrepancy is furnished by Thompson¹⁷ who has stated that certain cases of phlebitis and the ensuing complications may be the counterpart in women of thromboangiitis obliterans in men.

depletion of vitamins A and C in tuberculosis. We have been working with the latter group and have reported in an earlier paper that vitamin A is utilized at an accelerated rate and that this rate of destruction seems to parallel the extent of the tuberculous process.⁹ Harris and Harter have also found profound vitamin A deficiency in tuberculosis.¹⁰ Almost universally workers have found a marked deficiency of ascorbic acid, and some have stated that this deficiency parallels the extent of the disease.^{1,11} The work reported here attempts to bring new light on the relation of tuberculosis to these two vitamins. It is based on blood tests made on a population of very different character from the Wisconsin population that we studied with the biophotometer.⁹

Selection of Subjects. Most of the subjects were patients attending the chest clinic of this institute for the first time. More than twice as many negroes as white people were tested; persons of Italian descent were the largest nationality group among the white patients. One-half of the negroes and one-third of the white people were dependent upon public assistance for their living. Many of the subjects had no breakfast before reporting at the clinic; and those that did have breakfast had little or no citrus fruit. The effect of breakfast on the ascorbic acid plasma level will be discussed later. Data on the first 100 subjects were accumulated by testing the first 5 new patients each day. Later laboratory facilities were improved so that *all* new patients were tested as they presented themselves. Although this work was done during two periods (April-May, and September-October 1940), we found there was no difference between the first 100 tested and the rest; so all data were pooled. In short, our population group comes from the economically underprivileged areas of Philadelphia where malnutrition in adults as well as children is most apt to occur. Both malnutrition and tuberculosis have a known high incidence in these areas.

Methods. Blood was drawn usually between 10 and 11 A.M. by venipuncture into syringes well oiled with heavy mineral oil to reduce the possibilities of hemolysis and aëration. It was transferred immediately to a specially made 25 cc. ground glass-stoppered centrifuge tube which contained a drop each of 30% potassium oxalate and 5% potassium cyanide for each 5 cc. of blood drawn. The sample was centrifuged immediately; plasma was collected and the 4 cc. portion used for the ascorbic acid test was deproteinized at once. The vitamin A and carotene in the plasma were determined by the Künle modification of the Dann and Evelyn method¹² which employs the Carr-Price reaction and the photo-electric colorimeter. Ascorbic acid was determined by reduction of 2,6 dichlorophenolindopheuol with metaphosphoric acid plasma filtrates in the Evelyn photo-electric colorimeter. The procedure used was essentially that developed by Kimble and Barbour¹³ at the Wisconsin General Hospital, which combines features of the techniques of Mindlin and Butler¹⁴ and Evelyn, Mallory and Rosen.⁵ Erythrocyte sedimentation rate was determined by the method of Cutler.³

Results of Vitamin A Tests on Blood Plasma. A. Staff Members. A group of 15 staff members composed of technicians, nurses and

conclusive. Nevertheless, certain clinical features of thromboangiitis obliterans are more readily accounted for on the basis of fungous infection than by other etiologic agents thus far proposed. It therefore seems of primary importance to look for and to treat persistently any evidence of dermatophytosis in the patient with thromboangiitis obliterans.

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VITAMIN A AND ASCORBIC ACID IN PULMONARY TUBERCULOSIS.

DETERMINATION IN PLASMA BY THE PHOTOELECTRIC COLORIMETER.*

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MALNUTRITION is a constitutional factor that affects resistance to tuberculosis.^{4,6} Since new objective methods are expanding our knowledge of nutrition rapidly, this field promises much aid in the study of resistance and susceptibility in tuberculosis. The nutritive status is one of many factors which make for resistance or susceptibility. It seems evident, too, that tuberculosis interferes with the normal nutritional balance of the individual. The effect of the disease on the needs for specific nutritive constituents such as minerals, proteins, fats, carbohydrates and vitamins, is being investigated. Of especial interest to us has been the finding of

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B. Non-tuberculous Patients. The results of testing the plasma vitamin A of the non-tuberculous patients as plotted in Figure 1, show a wider range than the staff group. This is to be expected, as these patients have dietary customs which range from the equivalent of the staff members' diets to the starvation diets of those in abject poverty. The fact that most of these patients are very poor probably explains the concentration of the observed readings in the borderline and pathologically deficient levels. Two very high values were observed. One of these may be accounted for by supplementary vitamin intake. The non-tuberculous patients represent

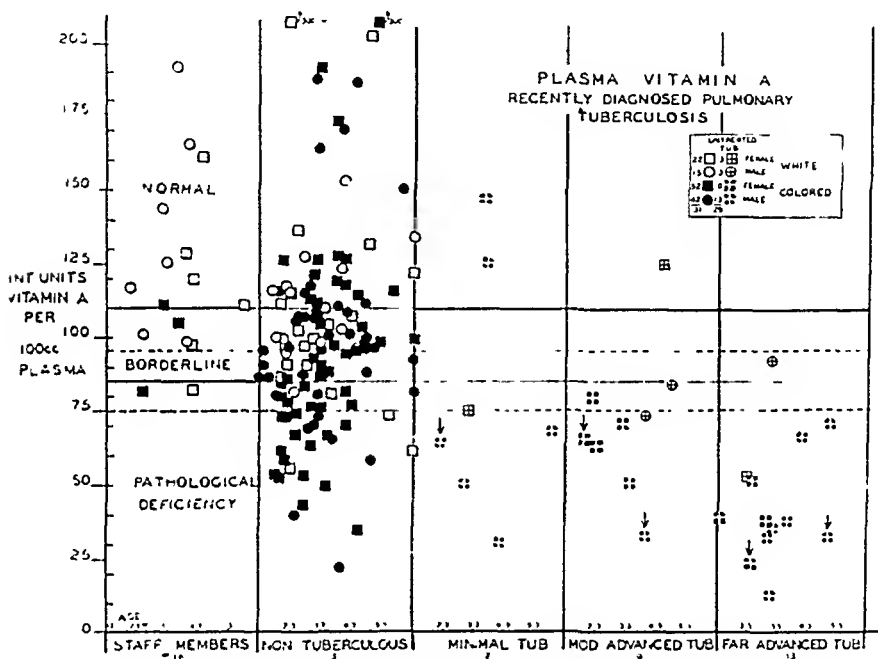


FIG. 1.—Plasma vitamin A observations on staff members, non-tuberculous and tuberculous patients at time of diagnosis. Note that no staff member is pathologically deficient while all but one of the far advanced patients are pathologically deficient. Black arrows indicate deaths.

all the patients coming to the clinic who did not have tuberculosis. Fifteen per cent had common colds and 35% had other upper respiratory infections. A large portion (27%) of the non-tuberculous patients had no known disease and were admitted to the clinic because of recent exposure to an active case of tuberculosis. Table 2 shows that the females of both races had the higher percentage of individuals with normal plasma levels and that they also had the higher percentage with pathologic levels. In Table 2, we believe the race difference in the percentage of patients in the pathologic level is important, as more than twice as many non-

physicians was tested as a normal control group to compare with all the patients. The economic status of the staff group was markedly different from the patients and supposedly all were eating complete diets except one who had an aversion to oranges but was eating an otherwise good diet. Both white people and negroes were represented. The individual observations are plotted in Figure 1. The range of the plasma level of vitamin A was classified in 3 groups as follows:

PLASMA LEVELS OF VITAMIN A IN INTERNATIONAL UNITS PER 100 Cc.

Sex.	Normal.	Borderline.	Pathologically deficient.
Male	110 and above	85-100	Below 85
Female	95 and above	75-95	Below 75

The lower level of normal shown for the females takes into account the sex difference in the plasma as described by Kimble^{13a} and Scalognne.¹⁷ These levels are empiric and undoubtedly will be changed to eliminate the borderline level, when sufficient work has been done to evaluate correctly the various blood levels. These 3 levels were chosen by us after careful consideration of our own data, and after consulting Dr. M. S. Kimble, Wisconsin General Hospital, who has had an experience of over 1000 tests. Some standard is needed to judge the degrees of depletion and to serve as a guide to those attempting to determine optimum nutrition.

In Tables 1 and 2 are listed the per cents of the staff members in each of the 3 plasma levels of vitamin A. None was pathologically deficient and only a few were in the borderline group. Since practically all of the staff members are in the normal group, we believe that our standards for vitamin A have been well chosen. The individual observations are plotted in Figure 1 (see Tables 1 and 2).

TABLE 1.—DISTRIBUTION OF WHITE AND NEGRO PATIENTS ON THE BASIS OF BLOOD LEVELS OF VITAMIN A.

Patient group.	No. of patients.	Normal %.	Borderline, %.	Pathologically deficient, %.
<i>White:</i>				
Non-tuberculous	36	61.1	27.8	11.1
Tuberculous just diagnosed	6	16.6	33.3	50.0
Tuberculous under treatment	13	38.5	23.1	38.5
<i>Negro:</i>				
Non-tuberculous	92	34.8	38.1	27.2
Tuberculous just diagnosed	23	8.7	4.4	87.0
Tuberculous under treatment	15	13.3	13.3	73.3
Staff members (both races)	15	73.3	26.7	0.0

TABLE 2.—DISTRIBUTION OF NON-TUBERCULOUS PATIENTS ON THE BASIS OF BLOOD LEVELS OF VITAMIN A AND RACE AND SEX.

Non-tuberculous patient groups.	No. of patients.	Normal, %.	Borderline, %.	Pathologically deficient, %.
White male	15	53.4	39.9	6.7
White female	21	66.7	19.0	14.3
Negro male	40	25.0	50.0	25.0
Negro female	52	42.3	28.9	28.9
Staff members (both races and sexes)	15	73.3	26.7	0.0

patients in the normal plasma level from 28.6% for the minimal to 0% in the far advanced tuberculous group, and the corresponding rise in the percentage of patients found pathologically deficient in vitamin A from 57.2% to 100%, shows a parallelism between vitamin A deficiency and the extent of tuberculous involvement. This verifies our earlier observation with the biophotometer.⁹ This same relationship of relative vitamin A depletion and stage of tuberculosis was observed when the data from the first 100 subjects were analyzed, and when we had tested approximately one-half the number of tuberculous patients. Two patients with far advanced,

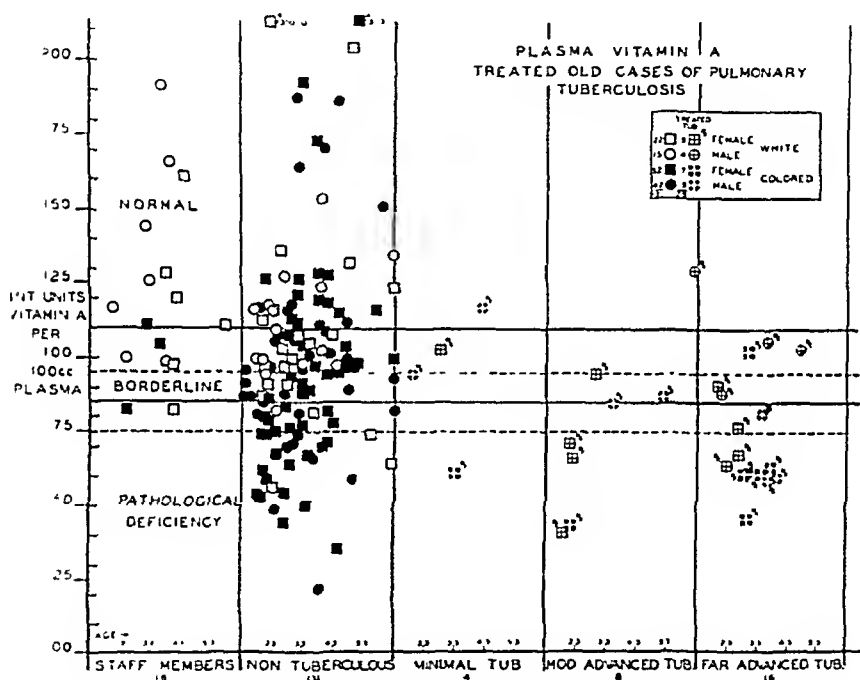


FIG. 2.—Plasma vitamin A observations on staff members, non-tuberculous and tuberculous patients receiving treatment.

2 with moderately advanced and 1 patient with minimal tuberculosis died in the first 3 months after diagnosis. Plasma observations on these 5 patients are marked with arrows in the figures. The two with far advanced tuberculosis that died had the next to the lowest values of plasma vitamin A. The patient with the lowest value in the far advanced group is still alive but critically ill in a hospital. The patient with the lowest value in the moderately advanced group is dead, as is the youngest patient, who had the fourth lowest value in the group. The youngest patient in the minimal group, with the third lowest plasma level of that group, is also dead. All 5 of these tuberculous patients had plasma levels of vitamin A below

tuberculous negroes (27.2%) were deficient as were white patients (11.1%). Comparing the non-tuberculous groups, 73% of the staff members, 61% of the white non-tuberculous patients, and 35% of the negro non-tuberculous patients, had normal plasma levels of vitamin A. This corresponds with the incidence of tuberculosis in these groups. The patients in the non-tuberculous group are the same in every other respect as the two tuberculous groups, since they are friends, relatives and neighbors of the patients and they constitute the reservoir in which tuberculosis develops. One of the non-tuberculous patients has developed a tuberculous process since the study began. No age difference in the plasma level of vitamin A was observed even when the data were plotted in other ways. If there is an age difference, it is slight and other forces in our population group are more powerful in determining the plasma level of vitamin A.

C. Tuberculous Patients Just Diagnosed. During our study, 29 patients entered the chest clinic for the first time and were diagnosed tuberculous and tested by us on the same day. These patients had had no therapy for tuberculosis, as their disease was previously unrecognized. Only 6 of these 29 patients were of the white race. The plasma levels of vitamin A of these patients are plotted in the 3 divisions of the extent of tuberculous involvement in Figure 1. In Table 1, the percentages of these patients falling into the 3 plasma levels reveal a marked drop in the number of individuals with normal plasma levels, viz., to 16.6% for the white and 8.7% for the negro race. This appears to be significant and shows a wide departure from even the low level of nutrition of the non-tuberculous group. There is a corresponding increase in the percentage of patients with pathologically low levels of plasma vitamin A; for the negroes it is 87.0% and for the white race it is 50.0%. This lowered vitamin A level means either: 1, disturbed physiologic processes, which may account for the lowered resistance of our tuberculous patients, especially the negroes; or 2, mere depletion of body stores with no other disturbance. The greater depletion of the negro patients is partly or perhaps wholly due to the smaller amounts present in the body before the disease is contracted.

TABLE 3.—DISTRIBUTION OF TUBERCULOUS PATIENTS ON THE BASIS OF BLOOD LEVELS OF VITAMIN A AND STAGE AND TREATMENT OF TUBERCULOSIS.

Tuberculous patient group.		No. of patients.	Normal, %.	Borderline, %.	Pathologically deficient, %.
Just diagnosed	Minimal	7	28.6	14.3	57.2
	Moderately advanced	9	11.1	22.3	66.6
	Far advanced	13	0.0	0.0	100.0
Under treatment	Minimal	4	50.0	25.0	25.0
	Moderately advanced	8	12.5	25.0	62.5
	Far advanced	16	6.3	31.2	62.5

In Table 3 are listed the percentages of patients in each plasma level for each stage of tuberculosis. The drop in the percentage of

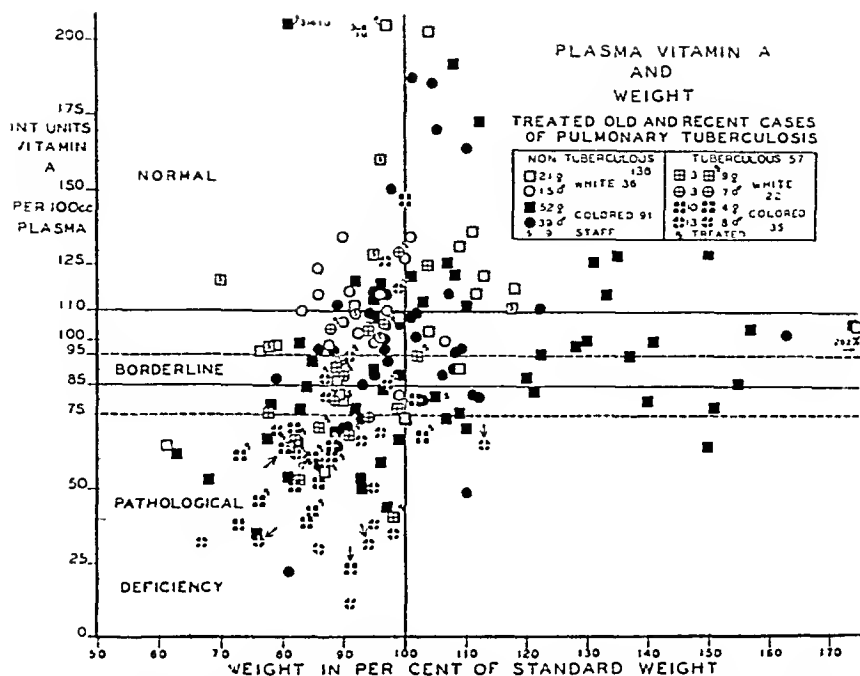


FIG. 3.—The relation between plasma vitamin A and per cent standard weight for all subjects.

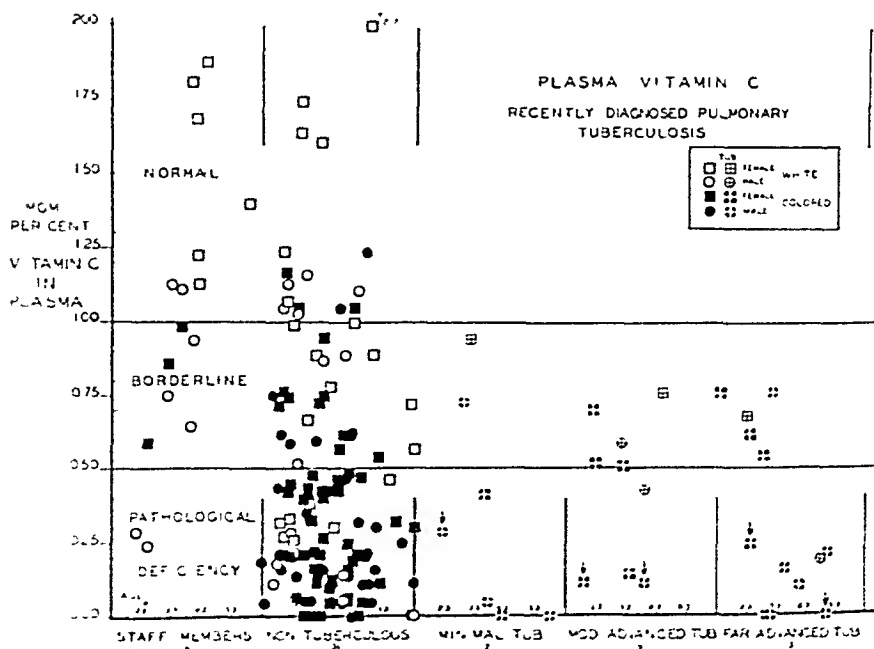


FIG. 4.—Plasma vitamin C observations on staff members, non-tuberculous and tuberculous patients at time of diagnosis.

70 I.U. per 100 cc. and died in 3 months. This strongly suggests that profound hypovitaminosis A in the tuberculous patient makes the prognosis worse.

D. Patients Receiving Treatment for Tuberculosis. The plasma level of vitamin A was determined for 28 patients receiving home bed rest. Most of these patients were receiving pneumothorax treatment in addition. No concerted effort with vitamin therapy was carried out; only 4 of these patients were taking cod liver oil, which was not given in sufficient amounts to raise their plasma levels to normal. The observations are plotted in Figure 2; Tables 1 and 3 give the percentages of patients in each of the plasma levels. Of these 28 patients 13 were of the white race. The percentages in the tables show that the patients under treatment have higher plasma levels than the just diagnosed patients. In Table 4 the same relationship of relative depletion that was observed with the just diagnosed group of tuberculous patients is preserved; namely, the percentage of pathologically deficient patients was greatest in the far advanced group and least in the minimal group. The racial handicap still exists for the negroes, as less than one-half as many have normal plasma levels as the white race. There have been no deaths in this group of patients while under observation.

TABLE 4.—DISTRIBUTION OF WHITE AND NEGRO PATIENTS ON THE BASIS OF BLOOD LEVELS OF ASCORBIC ACID ACCORDING TO SEX AND TREATMENT OF TUBERCULOSIS.

Patient group,	No. of patients.	Normal, %.	Border-line, %.	Pathologically deficient, %.
<i>White:</i>				
Non-tuberculous	Male 15	33.3	20.0	46.7
	Female 22	31.8	31.8	36.4
Tuberculous just diagnosed	Male 3	0.0	33.3	66.7
	Female 3	0.0	100.0	0.0
Tuberculous under treatment	Male 5	0.0	0.0	100.0
	Female 9	33.3	44.5	22.2
<i>Negro:</i>				
Non-tuberculous	Male 42	4.8	11.9	83.3
	Female 52	5.8	17.3	77.0
Tuberculous just diagnosed	Male 13	0.0	15.4	84.6
	Female 10	0.0	60.0	40.0
Tuberculous under treatment	Male 8	0.0	37.5	62.5
	Female 8	25.0	62.5	12.5

E. Plasma Vitamin A and Weight. In Figure 3 are plotted all the observations on plasma vitamin A against per cent of standard weight for each patient. All but 5 of the tuberculous cases are under 100% standard weight and 2 of these 5 are under treatment. Oddly enough the tuberculous individual with the highest per cent of standard weight (113%) was a "just diagnosed" individual who died within 3 months of tuberculosis. Only 1 non-tuberculous white woman was overweight, with more than 120% of standard, but there were 19 negroes overweight more than this figure. In Figure 3 we see that more overweight people had normal plasma

levels of ascorbic acid. It is more easily seen in the figures for the males than in the figures for the females.

In Figure 5 are plotted the same observations for the staff members and non-tuberculous patients as in Figure 4, but the other observations are for the tuberculous patients under treatment. In Table 4, *none* of the males of either race is shown to have a normal plasma level. Again, as with vitamin A, the treated tuberculous patients show better plasma levels than the just diagnosed tuberculous patients; in fact, the range of plasma levels is indistinguishable from the non-tuberculous group. The change for the females is

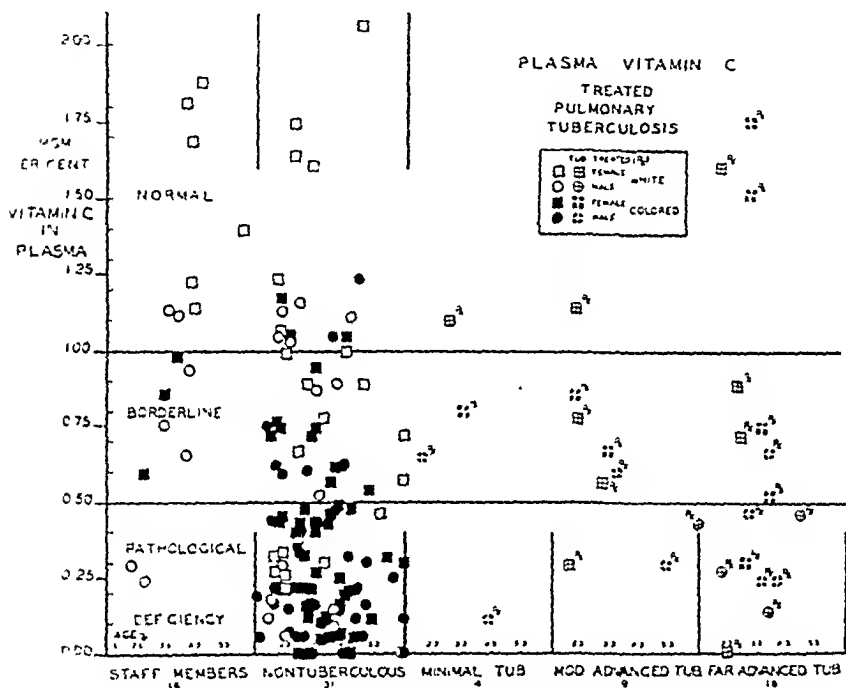


FIG. 5.—Plasma vitamin C observations on staff members, non-tuberculous and tuberculous patients receiving treatment.

particularly evident in the number and per cent that are now in the normal plasma level (Table 4). In Table 5 are listed the number of patients in each plasma level by stages of tuberculosis, and again we see the rough parallelism between depletion and extent of tuberculous involvement.

B. Plasma Ascorbic Acid and Weight. In Figure 6 are plotted the individual observations of plasma ascorbic acid against per cent of standard weight for each patient. Eleven of the 28 subjects with a normal level of ascorbic acid were underweight, weighing less than 90% of standard weight. Of the 204 subjects, 37 were overweight, weighing more than 110% of standard weight; 26 of these 37 over-

levels of vitamin A than did those who were underweight, and 9 overweight patients had pathologically low levels of plasma vitamin A. Obviously overweight individuals are not necessarily "well nourished" with respect to vitamin A.

F. Results of Carotene Tests on the Plasma of All Patients. The plasma carotene levels of the various groups of patients will be reported in a separate paper together with the results of other work with carotene.

Results of Ascorbic Acid Tests on Plasma. A. All Patient Groups. In Figure 4 are plotted the observations on the plasma level of ascorbic acid for each of the subject groups. The plasma range of ascorbic acid levels is divided into 3 groups; normal, borderline and pathologically deficient. Some workers would place the limit of the normal group at 0.7 mg. per 100 cc. of plasma,^{8,12} but we have found no reason to change the standard of 1 mg. per 100 cc. We realize that this standard has been set empirically and that the true limit of normal is yet to be determined. Almost all workers agree that the prescorbutic zone or pathologically deficient zone is below 0.5 mg. per 100 cc. Using these standards, only 50% of the staff members had plasma levels in the normal range, 37.5% had borderline levels, and 12.5% were pathologically deficient.

The staff members in the borderline and pathologically deficient groups (except one) were used in another experiment in which they were given orange juice* equivalent to 250 mg. of ascorbic acid daily. The staff member with the lowest ascorbic level was known to have an aversion to oranges. When tested 3 weeks later, all had normal plasma levels. This would indicate that their dietary intake of ascorbic acid had been too low and that our standard levels are well chosen.

The non-tuberculous patients have a wider range of plasma levels of ascorbic acid than the staff members and there is a gross difference in the distribution of observed levels as shown in Figure 4. A little over 30% of the white patients (both sexes) had normal plasma levels, as compared with 5 to 6% for the negroes (Table 4). Forty-seven per cent of the white males and 36% of the white females had pathologically low levels, while 83% of the male negroes and 77% of the female negroes had pathologic levels.

The just diagnosed tuberculous subjects had even lower levels of ascorbic acid. *None* had a normal plasma level (Fig. 4, Table 4); however, in this markedly deficient group the females of both races show levels higher than the males. In Table 6 are listed the number, instead of the usual per cent of individuals, in the 3 plasma levels, since the number of subjects became small when divided on a sex basis. There is a rough parallelism between the extent of the disease and the number of individuals with pathologically low

* Courtesy of California Fruit Growers Exchange.

corner are plotted the observations on patients with pathologically deficient plasma levels of both vitamins A and C. All 5 of the patients that died within 3 months after being diagnosed were in the latter group (Fig. 7).

In Table 6 are listed the number and per cent of the patients in each group that have normal plasma levels of both vitamins and pathologically low levels of both vitamins. The per cent of patients in each group with a normal plasma level of only one vitamin is also given, and, conversely, the per cent with a pathologically deficient plasma level of only one vitamin is given. The 16 patients that

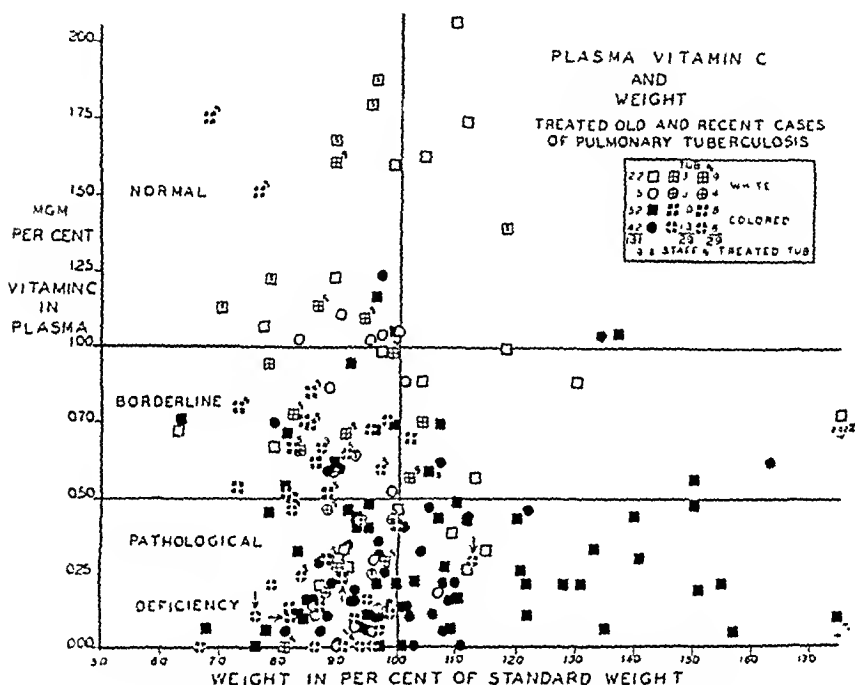


FIG. 6.—The relation between plasma vitamin C and per cent standard weight for all subjects.

had a normal plasma level of both vitamins were largely made up of staff members and white females (Table 6). The 43 patients with plasma levels revealing pathologic deficiencies of both vitamins were largely negroes, 14 females and 20 males. This shows a marked difference in the nutrition of the white and negro races in our population group.

Plasma Ascorbic Acid and Erythrocyte Sedimentation Rate. Since many far advanced cases of tuberculosis show a profound lack of ascorbic acid and have a high erythrocyte sedimentation rate, one might suspect a cause and effect relationship. In Figure 8 are plotted the plasma ascorbic acid observations against the erythro-

weight subjects had plasma ascorbic acid values in the pathologically deficient level, and 18 of the 26 were female non-tuberculous negroes. This observation that 26 of the 37 overweight subjects had pathologically low plasma levels of ascorbic acid shows that overweight patients are not always "well nourished" in regard to ascorbic acid.

TABLE 5.—TUBERCULOUS PATIENTS GROUPED ON THE BASIS OF BLOOD LEVELS OF ASCORBIC ACID AND SEX, STAGE AND TREATMENT OF TUBERCULOSIS.

Patient groups.	Males, No. of patients.			Females, No. of patients.		
	Normal.	Border- line	Patho- logically deficient.	Normal.	Border- line.	Patho- logically deficient.
Just diagnosed:						
Minimal	0	1	4	0	1	1
Moderately advanced	0	1	2	0	4	2
Far advanced	0	1	7	0	4	1
Under treatment:						
Minimal	0	1	1	1	1	0
Moderately advanced	0	1	2	1	4	1
Far advanced	0	1	6	3	4	2

TABLE 6.—PERCENTAGE OF PATIENTS IN EACH PATIENT GROUP WITH NORMAL PLASMA LEVELS AND PATHOLOGIC PLASMA LEVELS OF VITAMIN A, VITAMIN C, AND BOTH VITAMINS A AND C.

Patient group.		Total No.	Plasma level of—					
			Vitamin A.		Vitamin C.		Both vitamins A and C.	
			Normal, %.	Patho- logical, %.	Normal, %.	Patho- logical, %.	Normal, %.	Patho- logical, %.
Staff members		15	73 3	0 0	50 0	12 5	47 0	0 0
Non-tuberculous	White	Male	15	53 4	6 7	33 3	46 7	13 0
		Female	21	66 7	14 3	31 8	36 4	23 8
	Negro	Male	40	25 0	25 0	4 8	83 3	0 0
		Female	52	42 3	28 9	5 8	77 0	0 0
Tuberculous just diagnosed	White	Male	3	0 0	66 7	0 0	66 7	0 0
		Female	3	33 3	33 3	0 0	0 0	0 0
	Negro	Male	13	7 6	92 4	0 0	84 6	0 0
		Female	10	10 0	80 0	0 0	40 0	0 0
Tuberculous under treatment	White	Male	4	75 0	0 0	0 0	100 0	0 0
		Female	9	22 3	55 5	33 3	22 2	11 1
	Negro	Male	8	12 5	62 5	0 0	62 5	0 0
		Female	7	14 3	85.6	25 0	12 5*	14 3

* Eight patients.

Percentages in this table do not add to 100% because patients with borderline plasma levels of either or both vitamins are not included.

Plasma Ascorbic Acid Versus Plasma Vitamin A. In order to study the distribution of patients with multiple vitamin deficiencies, all observations on the plasma vitamin levels are plotted against each other in Figure 7. We note that the upper right hand corner is the region where observations are plotted on patients that had a normal plasma level of both vitamins A and C. In the lower left-hand

cyte sedimentation rate for each patient. A few patients with high normal plasma levels of ascorbic acid also had normal erythrocyte sedimentation rates, and also a few with normal ascorbic acid plasma levels had rapid erythrocyte sedimentation rates. It is true that the largest group of patients had an abnormally high erythrocyte sedimentation rate and a pathologically low plasma level of ascorbic acid, but 32 patients (16%) had pathologically low plasma levels of ascorbic acid and had a normal erythrocyte sedimentation rate. This, we believe, shows that the ascorbic acid deficiency and a rapid erythrocyte sedimentation rate may coexist but they *may also exist independently*.

The Effect of Breakfast on the Plasma Levels of Vitamins A and C. Five male negroes were studied to determine the effect of breakfast on the plasma levels of both vitamins A and C. Three of the 5 had come to the clinic without breakfast and the other 2 had breakfast without fruit. All 5 were bled on entrance and were immediately given 100 mg. of crystalline ascorbic acid* in 2 ounces of distilled water by mouth. This was the equivalent of a good breakfast of fruit containing ascorbic acid. One and one-half hours later they were bled a second time. The curve of the plasma level of ascorbic acid reaches a peak at about 3 hours after eating according to our data, which agree with those of Farmer and Abt.⁷ At one and a half hours the rise is about one-half as great as it is at the peak. All 5 patients had pathologically low levels of plasma ascorbic acid and failed to show any appreciable rise in their plasma level in one and a half hours. The rise for each patient was 0.04, 0.01, 0.08, 0.02 and 0.01 mg. per 100 cc. from 0.13, 0.17, 0.26, 0.00 and 0.06 mg. per 100 cc. plasma ascorbic acid, respectively.

These 5 patients were given no additional vitamin A and the 2 that had breakfast, with some vitamin A in the butter and cream, were compared to the 3 without breakfasts. One of the 2 with breakfast showed no rise in his plasma vitamin A 3 hours after eating. The other patient with breakfast was not bled at the time of eating but was bled 3 $\frac{3}{4}$ and 5 $\frac{1}{4}$ hours after eating. His last bleeding showed 63.5 I. U. per 100 cc. plasma while the first one showed only 41.8 I.U. per 100 cc. plasma. This boost, however, was not sufficient to raise his blood level from the pathologically deficient group. The 3 patients without breakfast changed their plasma levels very little in 1 $\frac{1}{2}$ hours. The changes in vitamin A were from 42.6, 57.3 and 108.0 to 45.4, 63.5 and 110.2 I.U. per 100 cc. plasma respectively. The slight rise in each case is insignificant, although the last case was boosted into the normal plasma group.

A healthy subject (H.G.) was given a breakfast including orange juice to the equivalent of 100 mg. of ascorbic acid and was bled at 1 $\frac{1}{2}$ hour intervals. One and a half hours after eating, his plasma level had risen from 1.34 to 1.46%. Three hours after eating it

* Courtesy of Merck & Co.

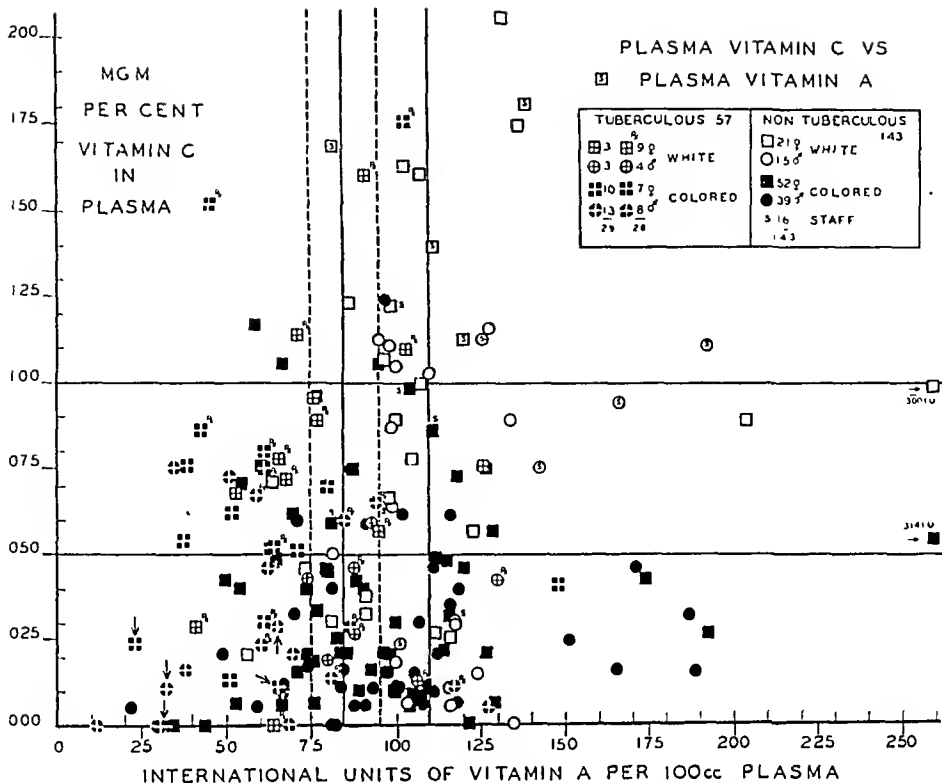


FIG. 7.—Plasma vitamin C plotted against vitamin A. The vertical and horizontal lines demarcate the plasma levels for each vitamin as before. Note that those individuals with normal plasma levels of both vitamins, in the upper right corner, are largely staff members and non-tuberculous white females. Those individuals with low levels aggregated in the lower left include the bulk of the tuberculous patients. Note especially that the 5 tuberculous patients who died had pathologically low levels of both vitamins.

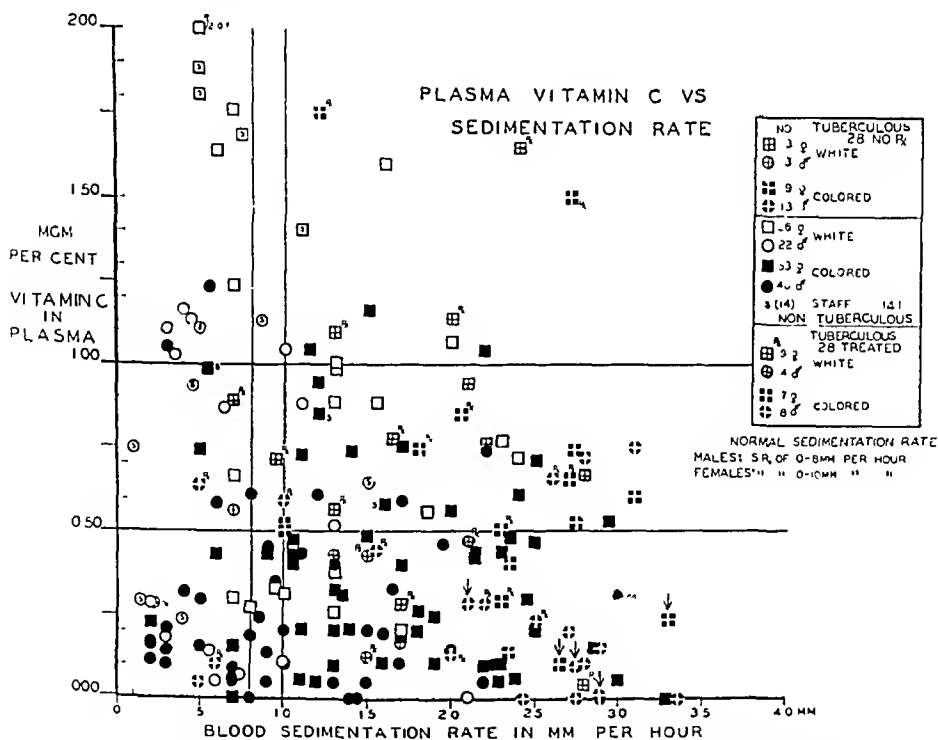


FIG. 8.—The relation between plasma vitamin C and blood sedimentation rate for all subjects. (843)

the negro males. Our figures are too small to prove such a contention definitely, but the data point out the possibility of a sex difference.

McConkey¹⁵ has shown that vitamin A and ascorbic acid play a rôle in the resistance to tuberculosis, as the incidence of intestinal tuberculosis was less in the treated group. The extensive work of Sweany *et al.*¹⁸ also shows that ascorbic acid has therapeutic value in tuberculosis. Osborn and Gear¹⁶ have pointed out that resistance to tuberculosis parallels the animal's ability to produce its own ascorbic acid. Our data, however, would single out vitamin A as the vitamin more closely allied with resistance. The fact that the young female negro patient is more susceptible to tuberculosis and more apt to be deficient in vitamin A and more apt to have a better ascorbic acid level than the negro male, supports this claim. We do not mean by this that vitamin A nutrition should be considered without respect to the other nutritive constituents. Undoubtedly, the "sparing and sharing" relationship between the vitamins necessitates optimum nutritive levels of all the constituents to obtain maximum resistance to infections. What is optimum for resistance to infection may be different from the optimum nutritive level for growth and probably distinctly different from the minimum nutritive level necessary to meet our accepted growth standards. Our vitamin-deficient overweight patients warn against the folly of considering overweight patients necessarily "well nourished." Wetzels¹⁹ determination of "nutritional grade" takes into consideration only those nutritive constituents that affect a minimum standard of growth and does not consider the optimum nutrition which is best for all body functions including resistance to infections and growth. We can learn the importance of malnutrition in resistance to infections only by studying tuberculous patients' requirements of specific nutritional substances. We find that tuberculosis alters the normal nutritive balance of at least two substances: heavy demands are made on the body for vitamins A and C and these demands are in proportion to the extent of the disease.

Conclusions. 1. The level of vitamin A in the plasma of tuberculous patients was lowered in proportion to the extent of tuberculous involvement.

2. The level of ascorbic acid in the plasma was lowered with tuberculous involvement and reached prescorbutic levels with advanced tuberculosis.

3. Pathologic deficiency of both vitamins A and C appears to make the prognosis worse in tuberculosis.

4. Non-tuberculous patients in the dispensary population studied were malnourished in both vitamins A and C.

5. Patients receiving bed rest and pneumothorax treatment had more vitamins A and C in their plasma than patients just diagnosed.

was 1.66 mg. per 100 cc. and at $4\frac{1}{2}$ hours it had dropped to 1.45 mg. per 100 cc. In the first $1\frac{1}{2}$ hours the rise was 0.12 mg. per 100 cc. which was more than that of the best of the 5 patients, who had a rise of 0.08 mg. per 100 cc. The plasma vitamin A on the normal subject who ate 750 I.U. in milk and butter for breakfast was very stable. One and a half hours after eating it had changed from 133 to 129 I.U. per 100 cc. plasma, at 3 hours it was 139 I.U. and at $4\frac{1}{2}$ hours 136 I.U. of vitamin A per 100 cc. plasma.

All the variations with breakfast were greater with vitamin C, but were not sufficient to alter seriously our distribution of patients in the 3 plasma levels. More than one-half of our new patients come without breakfast and those that do have breakfast rarely have as much as we gave our 5 test subjects. As we have demonstrated, 100 mg. of ascorbic acid does raise the plasma level more in a subject that has a normal level than in one whose tissues are unsaturated. Any errors in placing the patients in the proper plasma levels would all be in one direction. The tendency would be to boost a few patients that belong in the next lower level into the normal and borderline groups. This boosting is insignificant, as it would also tend to make our figures show less malnutrition than actually exists, while, as they are, they show profound malnutrition of our population in respect to ascorbic acid and a less but severe malnutrition in respect to vitamin A.

We are aware that alcoholic beverages may free stored vitamin A and thus falsely high plasma levels may be observed. Those of our patients, however, that drank alcoholic beverages apparently had exhausted their body stores by previous indulgence, for their plasma levels were lower in most instances than the group average. One tuberculous patient was thought to have cirrhosis of the liver and his plasma level was very low.

Comment. The vitamin A level in the blood stream is fairly stable and not affected by meals with the usual amounts of vitamin A and carotene consumed. This means that blood samples may be taken at any time without any great error in the assessment of nutritional status. If the peaks of fat absorption are avoided (3 to 6 hours after eating) there is still less chance for error. Ascorbic acid plasma values show a rise following each meal, which is greatest at about 3 hours. Ascorbic acid, being water soluble, is stored much less than vitamin A, as has been shown by Crandon and Lund.² A fasting plasma level would be preferable whenever possible.

The sex difference in plasma level of vitamin A has been observed before by Kimble^{13a} and Scalongne,¹⁷ and our data would substantiate their observations and would support a similar claim for ascorbic acid. With vitamin A, the females have a lower average plasma level, while with ascorbic acid it is just the reverse. This is particularly noticeable in the negro females in each patient group; the number deficient in ascorbic acid was always less than among

I. *K Avitaminosis*. The first method may be described as pure dietary K avitaminosis. It was used accidentally by Dam,^{8a,b} by McFarlane, Graham and Richardson,¹⁹ by Holst and Halbrook¹⁵ and by Almquist and Stokstad.¹ It is effective on newly hatched chicks, ducklings and goslings. It was effective in a rabbit (Dam and Glavind^{9a} and in 12 of 76 rats (Greaves¹¹). Early attempts to use the method in man failed (Dam and Glavind^{9b}) but recently Kark and Lozner¹⁷ reported success in 4 patients. Hemorrhagic disease of the newborn is regarded by Quick^{22c} as a simple K avitaminosis.

TABLE 1.—EXPERIMENTAL METHODS OF PRODUCING HYPOPROTHROMBINEMIA.

Method.	Species in which it is known to be effective.	Time required in first species mentioned.	Response to vitamin K.	
			Without bile salts.	With bile salts.
I. Dietary K avitaminosis	Chicks, rats, rabbits and man	4 to 14 days	Excellent	Excellent
II. Biliary fistula	Rats, dogs and man	21 to 28 days	Slight	Excellent
III. Common duct obstruction	Rats	21 to 28 days	Slight	Excellent
IV. Phosphorus poisoning	Dogs	12 hrs.	Poor	Poor
V. Chloroform anesthesia	Dogs	12 hrs.	Poor	Poor
VI. Carbon tetrachloride poisoning	Dogs and rats	12 hrs.	Poor	Poor
VII. Sweet clover disease	Cattle and rabbits	...	Good	...
VIII. Hepatectomy	Dogs and cats	1 hr.	Poor	Poor
IX. Liver massage	Dog	24 hrs.		
X. Changes in the circulation of the liver	Dog	2 to 4 wks.		

Times are approximate and subject in most instances to individual variation. A poor response indicates that little or no improvement results from vitamin K therapy.

II. *Sweet Clover Disease*. Sweet clover disease of cattle is associated with a hemorrhagic tendency which Roderick²⁴ showed to be due to a hypoprothrombinemia. Quick^{22a} has made a study with "spoiled" sweet clover hay on rabbits and believes that the toxic material destroys prothrombin directly and that the effect is not due to liver damage. The difficulty of extending observations on sweet clover disease lay in the fact that the toxic clover hay was not always available.

III. *Biliary Fistula*. A third method consists in diverting the bile from the intestinal tract by a complete internal or external biliary fistula. An internal fistula established by anastomosis of the gall bladder to the pelvis of the right kidney in the manner described by Kapsinow, Engle and Harvey¹⁶ was employed by Hawkins and Whipple.¹⁴ A hemorrhagic diathesis gradually developed in their animals over a period of from 2 to 4 months. Later Hawkins and Brinkhous¹³ showed that the hemorrhagic tendency produced by this method was due to a decline in the plasma prothrombin concentration. Several other investigators have since used this method for producing hypoprothrombinemia. It is often very slow. Two animals in this laboratory failed to show any striking change in prothrombin concentration 15 weeks after the establishment of a complete internal biliary fistula, of the type just described.

6. Females (white and negro) had less vitamin A and more ascorbic acid than males.

7. Ascorbic acid deficiency and rapid erythrocyte sedimentation may coexist but they also exist independently.

8. No age difference in the amount of vitamin A in the plasma was observed.

9. Many overweight patients were found pathologically deficient in vitamins A and C.

10. Negroes were found to be more malnourished in both vitamins than were the white subjects.

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EXPERIMENTAL HYPOPROTHROMBINEMIA.

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THE study of a group of hypoprothrombinemic patients that did not respond to vitamin K or its potent synthetic substitutes has led us to review the experimental knowledge of hypoprothrombinemia in the hope of defining the vitamin K-fast group of patients on an etiologic basis and in the hope of finding an effective therapeutic regimen.

A reduction in the concentration of the plasma prothrombin has been effected experimentally by at least 10 different means (Table 1). This laboratory has had first-hand experience with 6 of them.

corresponded somewhat to the extent of the operation but that there were rather wide individual variations. Complete hepatectomy is followed by a precipitous fall in the plasma prothrombin concentration in dogs as was shown by Andrus, Lord and Moore³ and by Warren and Rhoads.³⁰

IX. *Liver Massage.* Moderate declines in prothrombin concentration have been produced by simple massage of the liver through laparotomy wounds (Lord¹⁸).

X. *Disturbances in the Circulation of the Liver.* Finally, disturbances in the circulation of the liver may, at times, result in pronounced changes in the prothrombin level, as in some of the dogs hepatectomized by us according to the method of Mann as described by Markowitz.²⁰ The first stage of hepatectomy by this method consists in anastomosing the portal vein to the inferior vena cava and ligating the latter cephalad from the anastomosis. After allowing a period of 4 weeks for the establishment of adequate collateral circulation the portal vein is ligated cephalad from the anastomosis. The actual removal of the liver is carried out 3 weeks after the second stage. Two of the animals in which hepatectomy was done by this method had plasma prothrombin concentrations respectively of only 40% and 45% of normal at the beginning of the third stage.

The Basic Mechanisms by Which Hypoprothrombinemia Develops. Before discussing some of these methods in greater detail the mechanisms by which hypoprothrombinemia is produced experimentally may be rapidly reviewed. The first is simple K avitaminosis, the second a lack of bile salts in the intestinal tract resulting in a conditional K deficiency, due to the failure of absorption of the vitamin, the third is the unexplained action of a toxin on the plasma prothrombin and the fourth is deficient prothrombin production due to damage to the liver. So far, hypoprothrombinemia due to an inability of the wall of the small intestine to absorb vitamin K has not been reported in animals, although it has been postulated as the cause of hypoprothrombinemia in patients with sprue and celiac disease (Butt, Snell and Osterberg⁷). The natural occurrence of human hypoprothrombinemia due to the direct action of toxic substances on prothrombin has not been reported.* There remain, therefore, three mechanisms of clinical significance on which experimental data are available, namely, lack of vitamin K, lack of bile salt in the intestine for its absorption, and liver damage.

The amount of time required for the production of hypoprothrombinemia by any given method in the experimental animal is to some extent indicative of the mechanism by which it is produced. The dietary methods usually require 4 days to 3 weeks. The bile de-

* The active principle of spoiled clover hay (3-3' methylenebis 4-hydroxycoumarin) isolated in the department of Dr. K. P. Link has recently been employed by H. R. Butt, E. V. Allen and J. L. Bollman (Proc. Staff Meet. Mayo Clin., 16, 388, 1941) and in patients by J. B. Bingham, O. O. Meyer and F. J. Pohle (this journal, 202, 563, 1941).

Greaves and Schmidt¹² obtained a prothrombin deficiency in rats in a somewhat shorter time by transplantation of the common duct into the distal transverse colon. They demonstrated that the condition could be quickly corrected by the administration of vitamin K. Small doses were effective if bile salts were given, whereas very large amounts were necessary if bile salts were not administered. They, therefore, concluded that bile salts were required for the absorption of the vitamin. This was confirmed in the dog by Smith, Warner, Brinkhous, and Seegers²⁶ and has formed the basis for the treatment of hypoprothrombinemia in patients with obstructive jaundice or biliary fistula.

IV. *Common Duct Obstruction.* Simple obstruction of the common bile duct has not been a satisfactory method of producing hypoprothrombinemia in the dog. One of our dogs survived common duct obstruction for 13 weeks without developing any marked prothrombin deficiency. In the rat, however, Greaves and Schmidt¹² were able to produce hypoprothrombinemia by this method.

V. *Chloroform Anesthesia.* VI. *Carbon Tetrachloride Poisoning.* VII. *Phosphorus Poisoning.* These three means of reducing the prothrombin concentration in animals are so similar that they may be considered together. The administration of chloroform anesthesia and of phosphorus given hypodermically were first studied by Smith, Warner and Brinkhous^{25a} who showed that a severe drop in the plasma prothrombin concentration occurred after 90 minutes of chloroform anesthesia. They observed further that the drop started in 12 hours and reached a maximum within 48 hours. If the animals survived, the prothrombin level then gradually rose to normal over a period of 5 or 6 more days. These authors called attention to a difference between the effect of chloroform on the prothrombin concentration and its effect on the fibrinogen concentration of the plasma. They found that the prothrombin level was affected more easily than was the fibrinogen concentration, that it declined more quickly and that it returned to normal more slowly than was the case with fibrinogen. Quick^{22b} reported that carbon tetrachloride exerts an effect on prothrombin comparable to that exerted by chloroform. These experiments were quickly interpreted as evidence that the liver produced prothrombin. Later work tended to confirm this view but it is unsafe to conclude that effects observed following the administration of hepatotoxic agents are mediated solely by damage to the liver since simultaneous injury to other body tissues cannot always be excluded. The hepatic injury which follows the use of such substances results in a reduction of bile salt synthesis and consequently may interfere with the absorption of vitamin K from the intestine.

VIII. *Partial Hepatectomy and Total Hepatectomy.* Partial hepatectomy was carried out in rats by Warner.²⁸ If 60% to 75% of the liver tissue of these animals is removed the prothrombin level declines. Warner found that the average decline of groups of rats

experiments the animal which received its bile showed less prolongation of the prothrombin time than did its mate which did not receive its bile.

TABLE 2.—BILE SALT CONTENT OF HEPATIC BILE COLLECTED FROM DOGS FOLLOWING CHLOROFORM ANESTHESIA.

Dog No.	Bile salt concentration first 24 hrs.* (mg. per 100 cc.).	Prothrombin time (sec.).	
		Before anesthesia.	24 hrs. after anesthesia.
296	4560	15	245
126	1240	14	24
194	1160	18	180

* Calculated as cholic acid.

Plasma prothrombin concentration was determined by the method of Quick (Am. J. Physiol., 114, 282, 1936). Except in the case of the hepatectomized dogs the prothrombin times were not converted to concentration in per cent of normal. It should be remembered that prothrombin time increases as the concentration of prothrombin falls. As the concentration is reduced from 100% the prothrombin time at first increases very slowly and then more and more rapidly.

TABLE 3.—EFFECT OF INTERRUPTION OF THE FLOW OF BILE TO THE INTESTINE ON THE DEGREE OF HYPOPROTHROMBINEMIA INDUCED BY CHLOROFORM ANESTHESIA.

Dog No.	Duration of anesthesia (min.).	Bile flow interrupted.	Maximum prothrombin time (sec.).
271	30	No	18
252	30	Yes	36
296	50	No	17
297	50	Yes	45
296	50	Yes	245*
297	50	No	100*
527	55	No	27
528	55	Yes	360
536	50	No	92
537	50	Yes	23

* Prothrombin determination 24 hours after anesthesia.

Additional evidence that the major part of the fall in the plasma prothrombin concentration following chloroform is not due to the bile salt deprivation is to be found in the observation that dogs prepared as has been described would regenerate prothrombin after the first 2 or 3 days even though all bile was sidetracked from the intestine subsequent to the time of the chloroform anesthesia (Table 4).

TABLE 4.—CHANGES IN PROTHROMBIN TIME FOLLOWING CHLOROFORM ANESTHESIA IN BILE FISTULA DOGS.

	Prothrombin time (Quick*) (sec.).	
	Dog No. 126.	Dog No. 194.
Before anesthesia	14 0	18 0
First day	21 0	180 0
Second day	50 0	43 0
Third day	21 0	19 0
Fourth day	0	0
Fifth day	0	0
Sixth day	0	0
Seventh day	14 0	
Eighth day	..	18.5

* Am. J. Physiol., 114, 282, 1936.

privation methods usually require 4 weeks to 4 months. The chemical methods of liver injury require 12 to 48 hours and following total hepatectomy the prothrombin level begins to fall almost at once. One cannot, of course, conclude that the same time intervals will be operative in man as in the experimental animals, but a sudden drop in plasma prothrombin concentration in a patient is suggestive evidence of the development of hepatic damage.

Damage to the hepatic parenchyma nearly always results in a diminished bile salt content of the bile so that two mechanisms may operate together when such damage is present. In cases in which hypoprothrombinemia develops rapidly it would seem probable that the hepatic injury *per se* plays the dominant rôle. That this is actually the case following chloroform anesthesia in dogs is shown by the following experiments:

Experiments to Determine the Mechanism of the Development of Hypoprothrombinemia Produced by Chloroform and Carbon Tetrachloride. Stock dogs, which had been kept on a diet of table scraps, were operated upon under ether anesthesia. The common duct was divided and both ends intubated with small rubber catheters which led through stab wounds to the surface of the abdominal wall where they could either be connected if the normal flow of bile was to be restored, or separated to sidetrack the bile and to facilitate the collection of specimens. The cystic duct in these animals was ligated with silk. After the animals had recovered from the operation and with the catheters connected so that bile flowed into the duodenum, chloroform anesthesia was given each dog. It was ascertained in some of the animals that the plasma prothrombin concentration fell mainly during the first 24 hours and in most dogs continued to fall during the second 24 hours. In other animals the tubes were disconnected and the bile collected externally in rubber balloons following the anesthesia. This bile was then analyzed for its bile salt content.* The figures are calculated in terms of cholic acid. The data are given in Table 2. It will be seen that an ample amount of bile salt very likely was entering the duodenum on the day in which the plasma prothrombin concentration fell most rapidly. On the second day bile salt production was usually impaired. It, therefore, was concluded that the observed fall was not due primarily to an interference with bile salt formation. However, interruption of the flow of bile may have some influence on the degree of the fall in prothrombin concentration as indicated by the data in Table 3. These dogs were operated upon and anesthetized in pairs. Following chloroform anesthesia the tubes of one animal of each pair were left connected to permit the flow of bile to the intestinal tract, whereas the tubes in the other animal were disconnected. In the case of Dogs 39-296 and 39-297 the experiment was repeated reversing the animals. In four out of five such

* We are indebted to Mr. Mitchell Prushankin for the bile salt determinations.

munication.³⁰ In all of these animals, except 1 dog which lived only a short time and received a transfusion shortly before the final specimen was taken, a fall in the prothrombin concentration was observed. In the dogs that lived over 4 hours, this decline was quite marked (Table 6). It was much more rapid than the accompanying decline in fibrinogen concentration (Table 7). The prothrombin determinations were carried out by the method described by Quick in 1936. As the results of this method may be influenced by severe reductions in the fibrinogen level, the effect of added fibrinogen solution prepared as directed by Smith, Warner and Brinkhous^{25b} was investigated. As Chart 1 shows, the results ob-

Dog 691
Effect of Added Fibrinogen on Prothrombin Determinations.

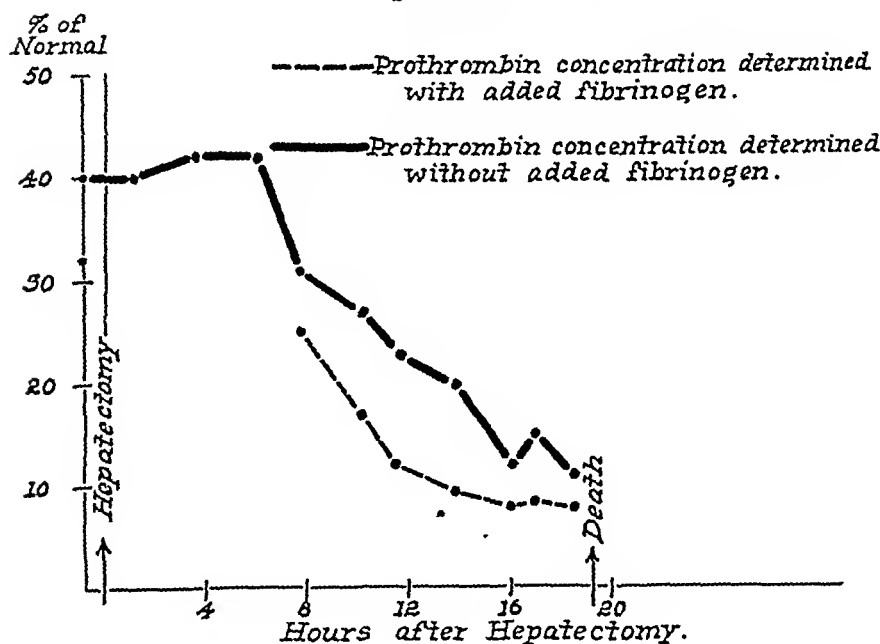


CHART 1.

tained with this modification of the Quick test for prothrombin were parallel to those obtained without the added fibrinogen. That the reduction in prothrombin concentration was not a simple dilution associated with intravenous infusions of glucose, was shown by determination of the cell volume index after centrifugation for 15 minutes at 2500 r.p.m. and by determination of the plasma protein concentration by the method of Barbour and Hamilton.⁶ Slight dilution did occur but this was not of sufficient degree to account for the rapid fall in the concentration of the plasma prothrombin (Charts 2 and 3).

A number of factors, other than the removal of the liver, might

That the effect of carbon tetrachloride administered orally is likewise not dependent upon an effect on bile salt production is shown in Table 5.

TABLE 5.—RECOVERY FROM HYPOPROTHROMBINEMIA INDUCED BY THE ORAL ADMINISTRATION OF CARBON TETRACHLORIDE IN A DOG WITH A COMPLETE EXTERNAL BILIARY FISTULA.

	Dog No. 126.
Dose of carbon tetrachloride (cc./kg.).	2 5
Prothrombin time:	
After 48 hours (sec.)	32
After 96 hours (sec.)	19

TABLE 6.—CHANGES IN PLASMA PROTHROMBIN IN HEPATECTOMIZED DOGS.

Dog No.	Method of hepatectomy.	Survival time (hrs.).	Preoperative prothrombin (% normal).	Last prothrombin determination before death (% normal).	Decline from pre-operative level (%).
379 . . .	Mann	6	80	10	87
877 . . .	Firor and Stinson	2	No prothrombin decline*		
891 . . .	Markowitz <i>et al.</i>	1	100	32±	68
892 . . .	Markowitz <i>et al.</i>	6	82	35	57
904 . . .	Markowitz <i>et al.</i>	5½	100	0	100
691 . . .	Mann	19	40	11	72
781 . . .	Mann	14	45	16	64
827 . . .	Mann	4	48	42†	12
				Average	58

* Dog had transfusion shortly before last specimen.

† Last specimen 2 hours postoperatively.

Two Additional Animals in Which Hepatectomy Was Performed in the Course of a Study of Cardiac Glucosides by Dr. Melvin Dresbach Also Showed an Early Prolongation of the Prothrombin Time.

Dog	Type of hepatectomy.	Prothrombin concentration immediately after operation (% normal).	Interval before death.	Last prothrombin determination before death (% normal).
Dog D . . .	1 stage	75	3 hrs. 45 mins.	20 0
Cat D . . .	3 stage	77	3 hrs. 30 mins.	12 5

TABLE 7.—CHANGES IN PLASMA FIBRINOGEN IN HEPATECTOMIZED DOGS.

Dog No.	Method of hepatectomy.	Survival time (hrs.).	Fibrinogen level.		
			Preoperative (gm./100 cc. of plasma).	Before death (gm./100 cc. of plasma).	Decline (%).
892 . . .	Markowitz <i>et al.</i>	6	0.508	0.407	20 0
904 . . .	Markowitz <i>et al.</i>	5½	1.019	0.400	61 2
691 . . .	Mann	19	0.297	0.229	22 9
781 . . .	Mann	14	0.805	0.779	3 3
827 . . .	Mann	4	0.511	0.226	55 8
				Average	32 6

Experiments on the Relation of the Liver to Prothrombin Formation and on the Significance of Hypoprothrombinemia Following Total Hepatectomy. We observed the effect of total hepatectomy on the plasma prothrombin level of 9 dogs and 1 cat. Most of these observations were reported in a preliminary form in a previous com-

have influenced the prothrombin concentration. Ether anesthesia, hemorrhage, and laparotomy were possible factors, the effect of which it seemed important to investigate. Table 8 shows the prothrombin times of dogs before and after ether anesthesia. Even when the ether was volatilized with but 15% of oxygen no striking reduction was obtained. In 1 animal in which a poor anesthetization was purposely carried out a slight fall in the plasma prothrombin concentration occurred.

TABLE 8.—THE EFFECT OF ETHER ANESTHESIA ON THE PLASMA PROTHROMBIN LEVEL.

Dog No.	Duration (hrs.).	Technique.	Remarks.	Prothrombin time.	
				Before ether (sec.).	Maximum following ether (sec.).
237	2	Gwathmey	Atmospheric air but cyanosis maintained	13	17.5*
237	2.75	Gwathmey	15% O ₂ and 85% N ₂	10	10
332	3	Gwathmey	15% O ₂ and 85% N ₂	13	12†

* 4 days later.

† Died of pneumonia on second day.

The effects of laparotomy and operation on abdominal organs other than the biliary tract are shown in Table 9 and the effect of hemorrhage on the prothrombin level is shown in Table 10.

TABLE 9.—THE EFFECT OF LAPAROTOMY FOR OPERATIONS ON ORGANS OTHER THAN THE BILIARY TRACT ON THE PROTHROMBIN TIME IN DOGS.

Dog No.	Prothrombin time.			
	Preoperative (sec.).	Immediately postoperative (sec.).	18 hrs. postoperative (sec.).	43 hrs. postoperative (sec.).
1	10	8	9	9.5
22	8	8	8	8
3	8	9	9	9
4	11	10.5	9	9

TABLE 10.—THE EFFECT OF HEMORRHAGE ON THE PLASMA PROTHROMBIN TIME OF DOGS.

	Prothrombin time (sec.).	
	Dog No. 700.	Dog No. 766.
Before hemorrhage	9½	14
After 12 hours	9½	13
After 24 hours	9½	13
After 48 hours	9½	12½

In each case the dog was bled until air hunger appeared. Approximately 350 cc. of blood were removed in each case.

These three factors do not explain the fall in plasma prothrombin concentration observed following extirpation of the liver.

Interference with the absorption of vitamin K would be expected to occur following hepatectomy. The cessation of bile salt forma-

Dog 791

Changes in Prothrombin, Fibrinogen, Plasma Protein and Hematocrit After Hepatectomy.

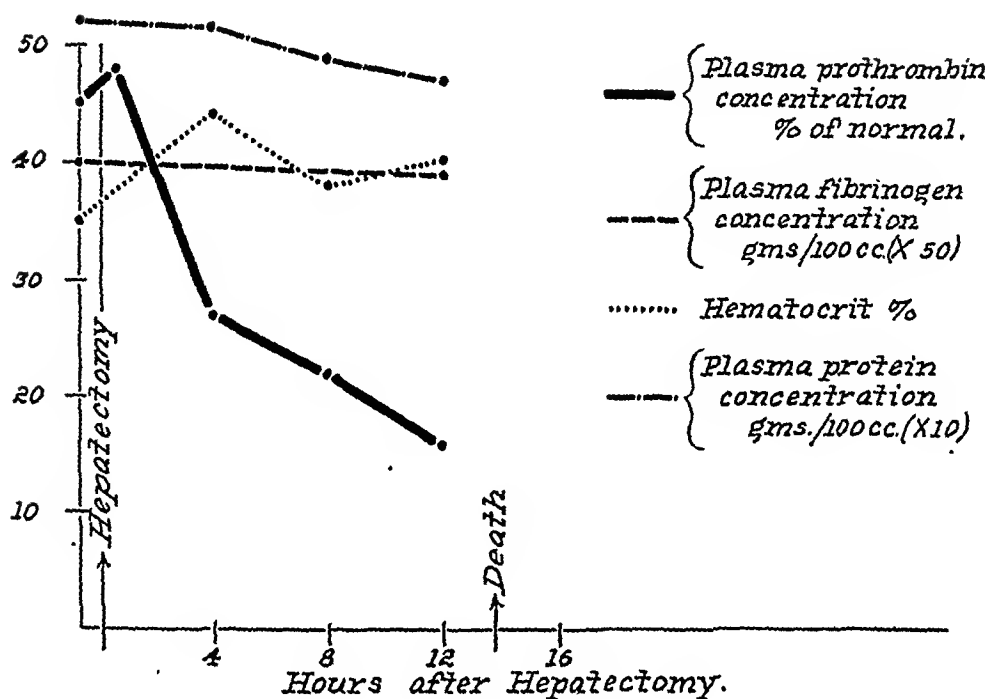


CHART 2.

Dog 691

Changes in Prothrombin, Plasma Protein, Hematocrit and Fibrinogen After Hepatectomy.

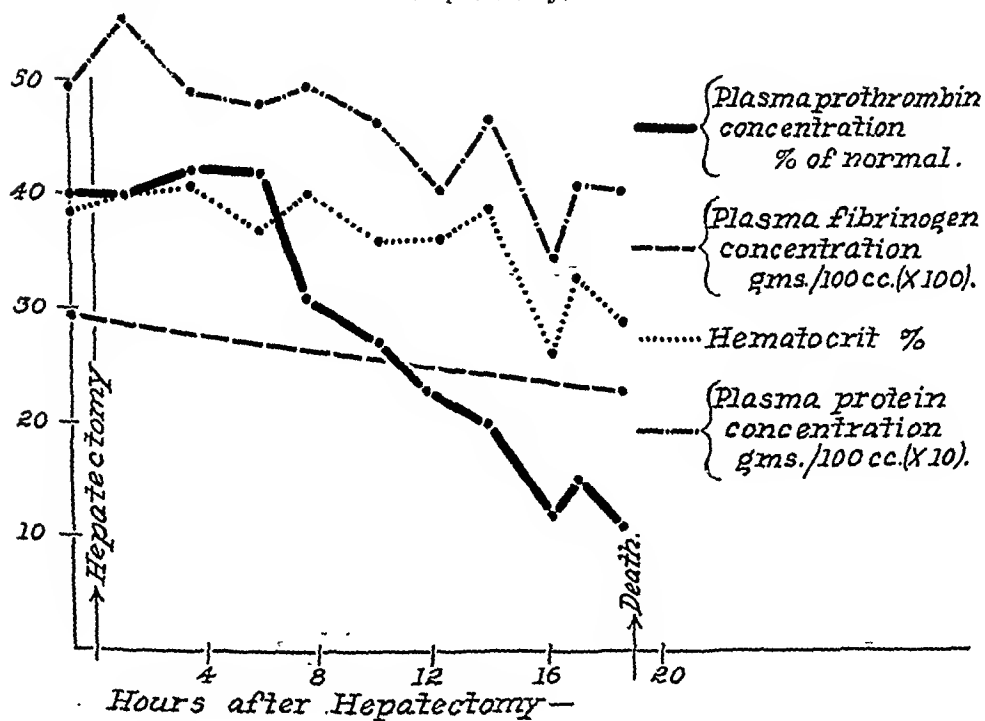


CHART 3.

observed after hepatectomy. This may indicate that there are other sources of prothrombin formation.

Without finding a particular locus for the destruction of prothrombin it is possible to explain its disappearance, at least partially, on the basis of observations of the plasma prothrombin in stored blood. Although this decline is slow in blood stored at 4°C . it occurs much more rapidly in blood allowed to stand at room temperature. Blood stored in an incubator at 37° shows even more rapid changes. Chart 4 summarized certain observations on the prothrombin concentration of oxalated human plasma stored in this way. The

The Influence of Temperature on the Disappearance of Prothrombin from Stored Human Plasma.

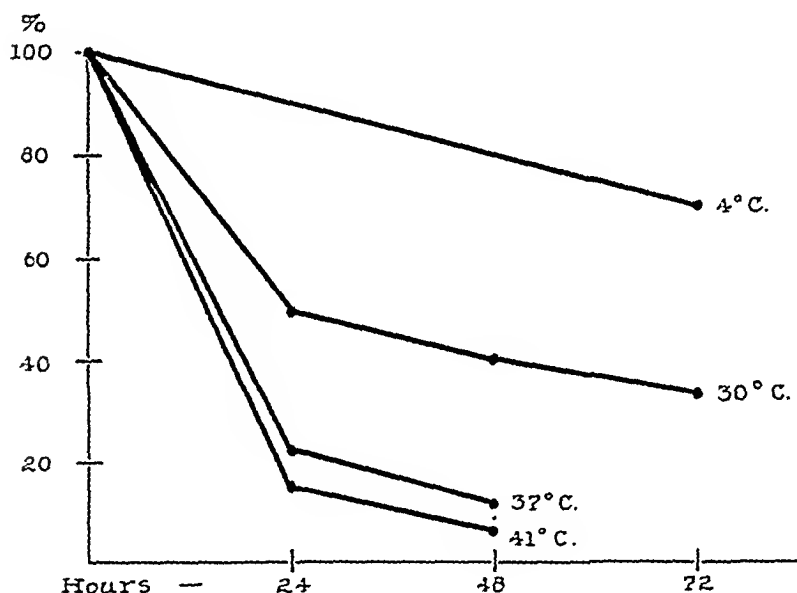


CHART 4.

decline is not as rapid as that observed in most hepatectomized dogs, but would correspond with the declines in some of the dogs observed in this laboratory.

The Effect of Vitamin K Therapy on Experimental Hypoprothrombinemia. Just as the time factor seems to vary with the mechanism by which hypoprothrombinemia is produced rather than with the particular means employed, so the response to therapy varies with the mechanism. To some extent at least the response of a hypoprothrombinemia of unknown etiology is indicative of the mechanism by which the condition has been produced.

tion would certainly interfere with its absorption and the necessary alteration in the venous drainage of the intestine might likewise interfere even if bile salts from other sources were supplied. The fact that a fall in plasma prothrombin occurred after one stage hepatectomy in healthy stock dogs in whom bile salt diversion does not produce a marked drop in prothrombin for many weeks indicated that this factor was not important.

In the experiments of Andrus, Lord and Moore³ bile salts and vitamin K were administered by enterostomy tube following hepatectomy without preventing the decline in prothrombin concentration. Despite the fact that Dam, Schoenheyder and Tage-Hansen¹⁰ failed to decrease blood coagulability in geese by exclusion of the liver from the circulation, it seems fair to conclude that in the dog, and probably also the cat, the synthesis of prothrombin in adequate quantities requires the presence of the liver. Whether the liver completes this synthesis or whether it is responsible for only one part of it cannot be stated with the data now available.

Considerable significance may be attached to the rate with which prothrombin disappears after removal of the liver because it implies constant and rapid destruction of this factor elsewhere in the body. It makes it unnecessary to postulate that substances, such as chloroform which cause rapid drops in the prothrombin level, do so by any direct destructive action on preformed prothrombin. It also points to a discrepancy between the cessation of prothrombin synthesis caused by absence of the liver and that due to absence of vitamin K. If vitamin K were chemically combined to form prothrombin one might expect a rapid decline in prothrombin when the supply of available vitamin K was used up instead of the relatively gradual decline usually observed. So many possibilities might explain this discrepancy that further speculation at this time seems useless. However, it is well to keep in mind that prothrombin need not necessarily be a single substance but might be a mixture of two or more substances having different origins, any of which might reach critically low levels independently of the others with a resultant decline in measurable prothrombin activity.

The site of prothrombin destruction has been investigated by Andrus, Lord and Kauer.² After comparing the plasma prothrombin concentration of arterial blood going to various organs with that of the venous blood coming from these organs, they concluded that prothrombin was destroyed in the lungs. In 85% of the dogs they found a mean decline in the pulmonary vein blood of 10.6% when compared to pulmonary artery blood. The determinations were done by the method of Warner, Brinkhous and Smith²⁹ and an accuracy of 3% was claimed for the method in duplicate specimens. As the blood probably passes through the lungs at an average rate of at least 30 times an hour the observations of Andrus, Lord and Kauer² would indicate a more rapid destruction than we have

response in normal persons makes one more critical of data obtained in K resistant patients with hypoprothrombinemia.

Summary. Ten means of producing hypoprothrombinemia in animals are briefly reviewed.

A comparison of experimental and clinical forms of hypoprothrombinemia point to three mechanisms for the development of hypoprothrombinemia which are common to both the experimental and clinical forms. They are a dietary K avitaminosis, a conditioned K avitaminosis due to absence of bile salts from the intestinal tract, and liver injury of sufficient degree to prevent synthesis of prothrombin at an adequate rate.

The mechanism by which the hypoprothrombinemia develops is characterized to some extent by the period required for its development. Exclusion of bile from the intestinal tract usually requires several weeks to a few months for the development of any marked degree of hypoprothrombinemia. Liver injury if it is produced rapidly is followed by a drop in the prothrombin level in a few hours. The dietary method has only been successful with regularity in poultry. An intermediate interval of 4 days to 3 weeks is required in chicks.

The three mechanisms are also characterized by the response of the hypoprothrombinemia which they produced to vitamin K. Hypoprothrombinemias due to dietary K avitaminosis are relieved by very small doses of the vitamin. Conditioned K avitaminosis due to a lack of bile salts from the intestinal tract does not respond satisfactorily to naturally occurring vitamin K in ordinary doses but will do so if bile salts are added. Hypoprothrombinemias due to hepatic damage of a degree sufficient seriously to retard prothrombin formation respond poorly or not at all to vitamin K and bile salts.

The last two mechanisms frequently operate together. Experimental evidence is presented indicating that the hypoprothrombinemia due to chloroform and carbon tetrachloride poisoning in dogs is primarily due to liver damage, although the presence of bile salts in the intestine appears to affect to some degree the extent of the fall in the prothrombin level.

Experimental data are also presented in support of the following points:

1. Chloroform anesthesia and carbon tetrachloride poisoning in dogs lead to a rapid drop in the plasma prothrombin level from which recovery occurs regardless of whether or not the bile reaches the duodenum.

2. Total hepatectomy in the dog and cat lead to a prompt decline in the plasma prothrombin level which cannot be attributed to: (a) hemorrhage, (b) ether anesthesia, (c) laparotomy *per se*.

3. A rapid decline in prothrombin may occur in human plasma *in vitro* at 37° C.

Simple K avitaminosis in chicks responds within a few hours to the oral administration of 2-methyl-1,4-naphthoquinone (Ansbacher⁴). Vitamin K in any form will effect a prompt response.

Bile fistula animals will respond well to oral vitamin K with bile salts. The response to bile salts alone is slower but does occur.

If the absorbing membranes were at fault one would expect a poor response to vitamin K and bile salts by mouth but a good response following the parenteral administration of vitamin K. In hypoprothrombinemia produced in the dog following chloroform anesthesia, 2-methyl-1,4-naphthoquinone intravenously did not produce an appreciable effect. Andrus, Lord and Moore³ have found that doses as large as 10,000 units of vitamin K have been without effect in influencing the prothrombin level of the hepatectomized dog. Bay⁶ reports decreasing the extent of the decline in the plasma prothrombin level in the dog following chloroform by giving large doses of 2-methyl-1,4-naphthoquinone but a considerable decline occurred nevertheless.

There is, therefore, presumptive evidence that in the type of hypoprothrombinemia in patients that is due to severe liver damage, a poor response will be obtained. Histologic evidence that liver damage was present in 3 patients with hypoprothrombinemia who failed to respond to vitamin K therapy has been presented.^{23a,b} Some authors have, however, expressed the opinion that by increasing the dosage of vitamin K in patients that did not respond to the usual dosage they were able to obtain a satisfactory response.²⁷ Investigation of this finding is difficult because the functional status of the liver may change rapidly and a sufficiently large number of clinical observations has not accumulated for statistical analysis.

The relationship between vitamin K and prothrombin is entirely obscure. They are different substances physiologically as well as chemically. Vitamin K has no activity when substituted for prothrombin in a clotting system and prothrombin preparations are only slightly beneficial when fed to K avitaminotic chicks (Dam, Schoenheyder and Tage-Hansen¹⁰).

If vitamin K has a mass action effect in the production of prothrombin, one would expect that quantities of it added to a normal diet might elevate the prothrombin level above normal. This hypothesis was tested in a group of miscellaneous surgical patients (Norris and Rhoads²¹) who received 6 mg. of 2-methyl-1,4-naphthoquinone daily with 15 grains of iron bile salts for varying periods of time without a significant increase in prothrombin concentration above the normal as determined by the Quick method and by certain modifications thereof. One cannot conclude from this study in relatively normal individuals that increasing the dose of vitamin K above the amount usually found adequate would not be of value in patients with liver damage but at least the failure to obtain this

dependent edema in malaria are the marked anemia, increased capillary permeability or a disturbance in the plasma proteins of the blood. The anemia of therapeutic malaria may be quite marked, as low as 2.5 million red cells, but it is unlikely that this is wholly responsible for the edema, since the latter may disappear fairly rapidly while the anemia persists. Increased capillary permeability with an increased hydrostatic pressure when the erect posture is maintained may play some part in the production of the dependent edema. It does not explain, however, the mechanism of the generalized edema. Disturbance of the colloids, especially the plasma proteins, may be an important factor since food intake is often diminished and weight losses of 10 pounds or more may occur during therapeutic malaria. A reduction in the plasma proteins, especially albumin, would change the osmotic pressure, affect the interchange of fluid between blood and tissues and thus produce edema. In order to test this hypothesis the studies described in this paper were undertaken.

Material. Seven male patients, ranging from 40 to 51 years, were hospitalized for the malarial therapy of general paresis. Physical examination and laboratory procedures revealed no other complicating diseases.

Methods. The patients had 10 to 13 paroxysms of malaria and were ambulatory between paroxysms. The malaria was terminated by the administration of 10 gr. of quinine sulphate 3 times a day for 1 week.

The daily hospital diet consisted roughly of the following: protein 80 gm., carbohydrate 315 gm., and fats 85 gm. When fever was present and food intake diminished, the daily diet was reinforced by the addition of at least 1 quart of milk and 2 eggs (protein 42 gm., carbohydrate 50 gm., and fat 52 gm.). After termination of the malaria, each patient was given a high vitamin, high calorie diet, and 20 gr. of ferrous sulphate daily. Sodium chloride was administered to 6 patients during malarial therapy as a result of the observations of Judd⁷ who felt that patients were better able to tolerate the fever when 10 gr. of the salt were given on those days when body temperature rose above 103° F. Larger doses than suggested by Judd were given: 5 patients received 4 gm., and 1 patient 6 gm. daily. The seventh patient (T. G.) received no sodium chloride during his malaria other than that present in the diet. The sodium chloride was omitted when malarial fever was terminated, with the exception of 1 patient (F. F.) who continued to receive 6 gm. daily for 6 days thereafter.

Studies were made of the hematocrit, red cell count and hemoglobin (Sahli) levels on venous blood samples in the resting state. In most instances the patient was afebrile at this time.

The total plasma protein was obtained by the determination of the total nitrogen by a modified micro-Kjeldahl method;⁸ the non-protein nitrogen by the method of Folin and Wu;⁹ the albumin and globulin by the sodium sulphate method of Howe;¹⁰ the fibrinogen by precipitation as fibrin by the method of Cullen and Van Slyke;¹¹ and the plasma chloride in 2 patients by a modification of the method of Van Slyke.¹² In the last series of studies (Patients F. F. and T. G.) the fibrinogen was precipitated as above, and the nitrogen content of the fibrinogen was determined directly. Potassium oxalate in the concentration of 2 mg. per cc. was used as the anticoagulant.

Results. Plasma albumin fell progressively as the malarial fever continued and even for a few days thereafter. The pre-febrile

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THE RELATIONSHIP OF HYPOALBUMINEMIA TO THE EDEMA OF MALARIA.

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EDEMA occurs quite often in patients undergoing therapeutic malaria. The edema is usually regarded as of cardiac origin, provided renal damage has not developed. However, there are a series of facts which makes this hypothesis unlikely, namely: the absence of other symptoms and signs of cardiac involvement, such as increased basal pulse rate, pulmonary râles, dyspnea, cyanosis and increased venous pressure; and the rapidity with which the edema disappears with or without rest in bed, restriction of salt and fluid intake or digitalis therapy.

Other factors which must be considered as possible causes of the

in 4 patients significant increases, in 2 patients a rise and then a fall, and in 1 patient a fall throughout.

The net result of the changes described above was a reduction of the total plasma proteins, since the increases in globulin and fibrinogen when present were insufficient to balance the reduction of albumin. Pre-febrile plasma protein values ranged from 6.88 to 8.2 gm. and fell to 5.03 to 7.3 gm., the maximum reduction being 28.5% (Patient F. F.).

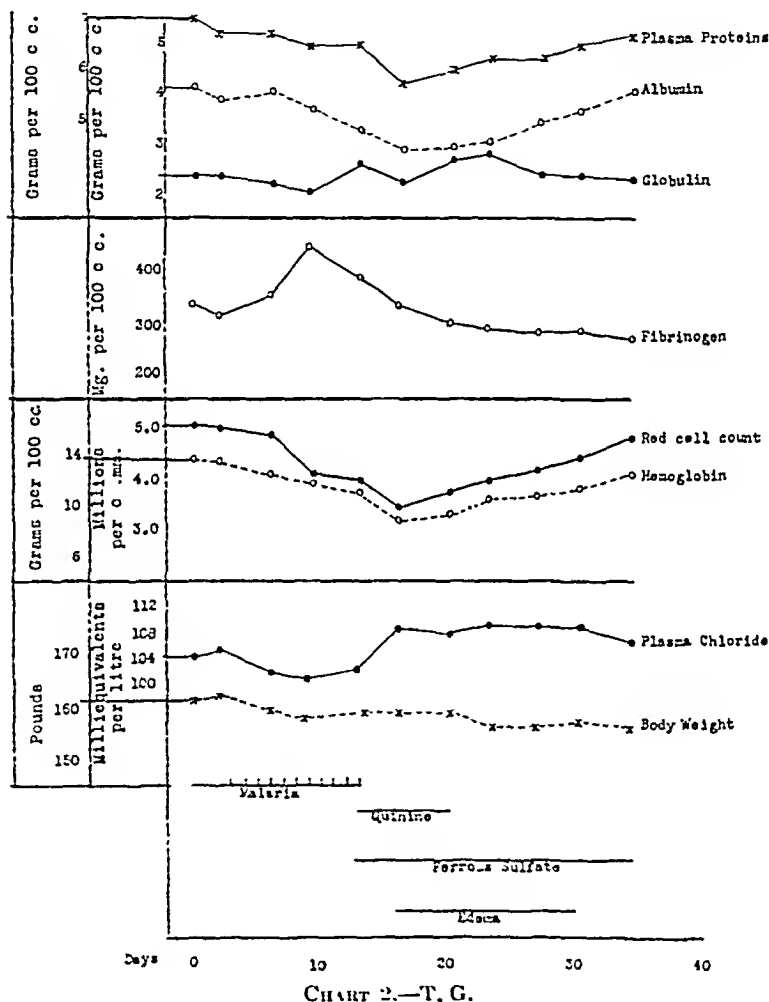


CHART 2.—T. G.

The fall in albumin ceased with the termination of the malarial fever by quinine or within a few days thereafter. The albumin rose to pre-febrile levels in 6 patients within 14 to 24 days. The return to normal in the seventh patient was quite slow, requiring

levels of 3.7 to 5.1 gm. fell to 2.23 to 3.4 gm., and in 6 of the 7 patients were reduced to less than the critical level of 3.1 gm. at which edema is said to occur in infections.¹² The reductions represented 30% to 40% of the original levels.

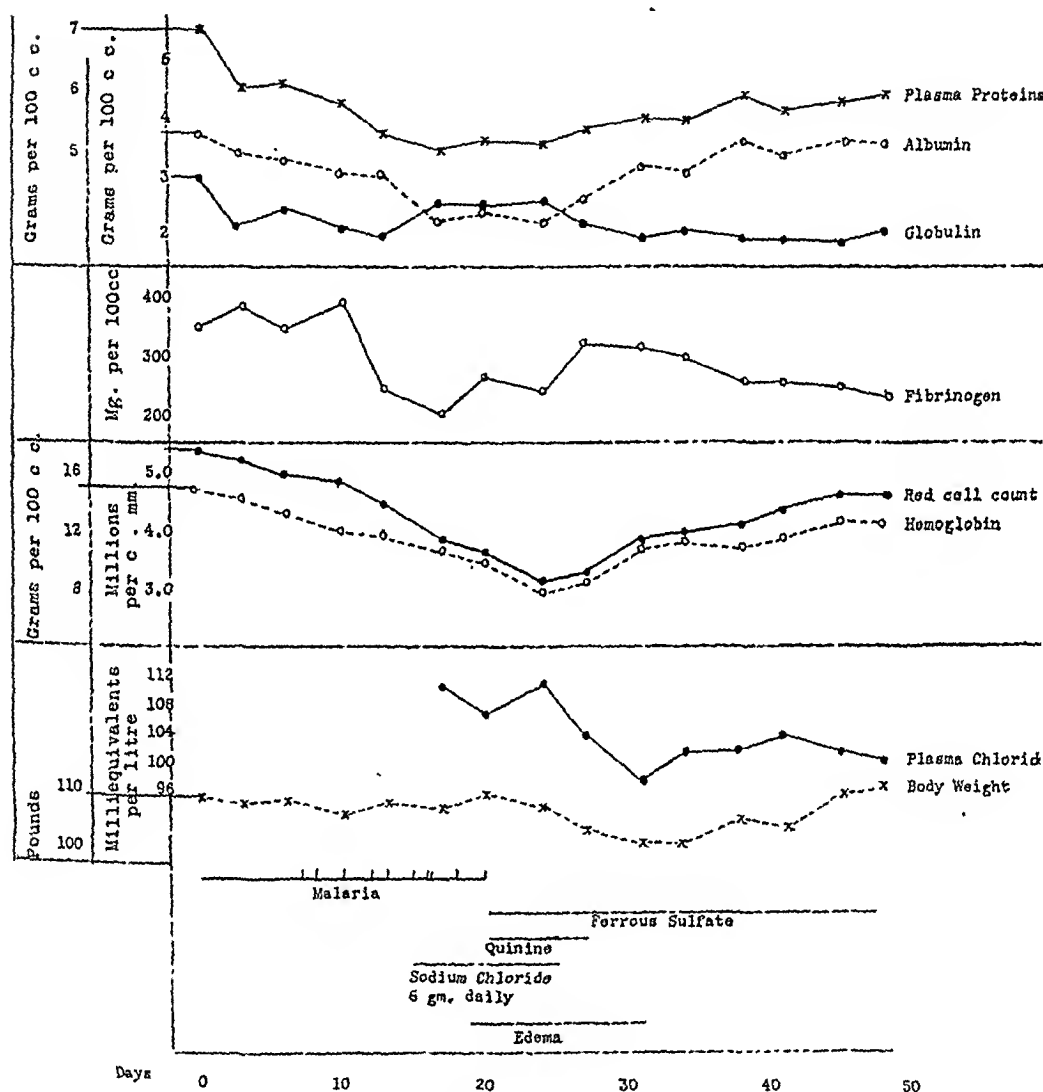


CHART 1.—F. F.

The globulin fraction, on the other hand, rose after a few paroxysms of fever, reaching its highest level (10% to 65% increase) at about the period that the albumin fraction showed its greatest decrease. The globulin changes of 2 patients differed, 1 (F. F.) showing a reduction of globulin, as great as 32%, throughout the malaria (Chart 1); and the second (T. G.) showing a progressive but less marked fall until the eleventh paroxysm (Chart 2).

Fibrinogen values did not show a consistent trend as did the albumin and globulin fractions. Considerable fluctuation occurred:

these regions.^{1a} Capillary permeability and electrolytic balance, especially the sodium ion, also play important parts. The fundamental cause of edema, however, is hypoproteinemia resulting in a reduction of the osmotic pressure of the serum proteins.¹¹ The appearance and the intensity of the edema parallel the reduction of the albumin fraction, rather than the total plasma protein values. Moore and Van Slyke¹⁰ found that edema was always present when albumin fell to 2.5 ± 0.2 gm. per 100 cc. of blood. Peters and Eisenman¹² found edema in more than one-half of 50 non-nephritic patients with infections when serum albumin was below 3.1%, and invariably when colloid osmotic pressure was less than 20 mm. mercury. Dehydration might prevent the occurrence of edema at these levels, whereas circulatory failure or stasis precipitated it.

Edema has been shown by some⁶ to occur when colloid osmotic pressure of the plasma was reduced to levels of 17 to 21 mm. of mercury, provided hydrostatic pressure was unchanged, and by others⁸ at osmotic pressures below 15 to 17 mm. of mercury. Melnick and coworkers,⁹ however, point out the inadequacy of colloid pressure measurements *in vitro* and of the determination of albumin and globulin for predicting the true osmotic pressure in man. In their opinion recent physico-chemical studies have disproven the major importance of the albumin fraction in preventing the formation of edema.

The results obtained in our patients during malaria bear out the importance of plasma albumin and osmotic pressure values in the production of edema. Albumin fell to the edema level of infections, 3.1 gm. per 100 cc. of blood, in 6 of the 7 patients. The osmotic pressure of the blood of these patients fell to 21 mm. or less. Dependent edema developed in 3 patients at albumin levels of 3 gm., 2.89 gm. and 2.23 gm., and at osmotic pressures of 20.4 mm., 19.2 mm., and 15.4 mm. mercury, respectively. An increase of 2.5 pounds in body weight occurred in a fourth patient at an albumin level of 2.73 gm. and an osmotic pressure of 19.5 mm. mercury. Disappearance of the edema accompanied by loss of body weight occurred in the first 3 patients concomitant with an increase in albumin to 4.3 gm., 3.7 gm., and 3.2 gm., and a rise in the osmotic pressure to 27.9 mm., 23.8 mm., and 20.5 mm. of mercury, respectively. The absence of clinical edema in the remaining 2 patients with low albumin levels does not necessarily imply that fluid retention, subclinical in type, had not occurred and was masked by the weight changes present during malaria. Thus, though marked generalized edema occurred in 1 patient (Chart 1), the maximum body weight was only $\frac{1}{2}$ pound greater than before malaria, the accumulated fluid balancing the tissue weight loss.

It is difficult to evaluate the importance of the malarial anemia as a contributing factor in the production of the edema. Edema occurred when anemia was most marked, usually at levels of 9.7 gm.

about 10 weeks. The increased globulin values, when present, persisted from 10 to 18 days. The fibrinogen returned to normal in about 1 week's time.

The albumin-globulin quotient of each patient fell during malaria: in 4 patients close to 1 and in the remaining 3 patients below 1. The quotient rose fairly rapidly toward pre-febrile levels after the termination of the malaria and as albumin increased.

The osmotic pressure of the plasma proteins (1% albumin equals 5.5 mm. of mercury: 1% globulin equals 1.4 mm. of mercury) fell progressively in each patient as the malaria fever recurred, the amount of fall depending on the reduced albumin values. Pre-febrile osmotic pressures ranged from 24.43 to 31.78 mm. of mercury and fell to levels of 15.91 to 23.04 mm. of mercury. In 6 patients the osmotic pressure fell below 21 mm. of mercury, at which level edema frequently occurs.¹² The osmotic pressure rose rapidly after the malarial fever was terminated, paralleling the increase in albumin.

Clinical edema developed in 3 of the 7 patients during malarial therapy. One patient developed dependent edema when albumin had fallen from a pre-febrile level of 5.1 to 3 gm., and while receiving 4 gm. sodium chloride daily. The edema disappeared after 10 days during which time the patient was ambulatory and the sodium chloride was omitted. The disappearance of the edema was accompanied by a rise of albumin to 4.3 gm. and a loss of 9 pounds in weight. A second patient (F. F.) developed dependent edema and edema of the face and hands when albumin had fallen from 3.67 to 2.23 gm. (Chart 1). The patient had received 6 gm. of sodium chloride daily for 4 days before the edema was noted and for 6 days thereafter. A rise in albumin to 3.2 gm. in 12 days was accompanied by disappearance of the edema, a loss of 7.5 pounds in body weight, and a fall in the plasma chlorides from 110.9 to 98.1 milliequivalents per liter (normal 99 to 106 milliequivalents). A third patient (T. G.) developed edema of the ankles and puffiness of the hands and face when albumin had fallen from 4.13 to 2.89 gm. (Chart 2). He had received no additional sodium chloride during therapy. The plasma chlorides, however, increased from 104.1 to 108.6 milliequivalents per liter when edema was first noted. The edema persisted for 14 days during which time albumin rose to 3.7 gm. but plasma chlorides remained unchanged. A fourth patient gained 2.5 pounds in body weight, but with no clinical evidence of edema when albumin had fallen from 4.37 to 2.73 gm. Albumin rose to 3.6 gm. within 3 days and body weight fell 2.5 pounds. The laboratory findings on each of the above patients revealed no evidence of nephritis as a result of the malaria.

Discussion. The important physical factors which determine the flow of fluid from the tissues into the blood stream and in the reverse direction are the osmotic and hydrostatic pressure of the fluids in

the capillaries would be increased. Veil¹⁶ found that when large amounts of sodium chloride were taken, a rise in blood sodium chloride and a great increase in blood water first occur, followed by a pouring out of salt and water into the tissues and a return of the blood chloride value to normal. Blood plasma volume may also be increased because of the secondary anemia present in malaria.⁴ The blood plasma volume of patients with Epstein's nephrosis, however, is diminished.⁴ In this condition plasma proteins, especially albumin, are considerably reduced, serum chlorides are above normal if altered at all and edema may be generalized and marked. The low plasma albumin and osmotic pressure values of patients during malaria are factors against the presence of a significantly increased blood plasma volume. Increased hydrostatic pressure does not occur, since signs of increased venous pressure are not seen.

Conclusions. 1. Marked disturbances with a reduction of the plasma proteins occur in malarial fever. Albumin values fall progressively to critical levels at which edema may occur. Globulin, as a rule, shows a progressive increase after the first few paroxysms, reaching its highest level at a time when albumin values are about lowest. Fibrinogen values fluctuate considerably and in 3 of 7 patients were reduced below pre-febrile levels.

2. The termination of malarial fever is followed by an immediate and continued rise of albumin and a delayed but progressive drop of globulin from its highest level so that normal values are obtained in from 10 to 24 days. Fibrinogen values return to normal within 1 week's time.

3. The albumin-globulin ratio falls rapidly during malaria reaching levels of 1 or below after 10 to 12 paroxysms have occurred.

4. The dependent or generalized edema occurring during the course of therapeutic malaria in patients free from renal damage or cardiac failure, is the result of a reduced osmotic pressure caused by a marked fall of the albumin fraction to levels of 3 gm. per 100 cc. or below.

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of hemoglobin per 100 cc. of blood and 3,500,000 red cells per c.mm. or less. Not all patients, however, develop edema at these levels. Peters and Eisenman¹² observed that edema occurred at a higher level of serum albumin (4%), and at a higher osmotic pressure (26 mm. of mercury) in patients with anemia (10.9 gm. hemoglobin per 100 cc. or less). Alteration of capillary pressure and increased capillary permeability from less perfect oxygenation were thought to play some part. The low red cell count was probably of importance, since it has been shown that red blood cells *per se* produce an osmotic pressure effect.¹¹

The daily intake of 4 to 6 gm. of sodium chloride during malaria is of importance, since the addition of large doses of sodium chloride (13.5 gm.) to hypoproteinemic animals frequently precipitates edema at albumin levels at which the animal was previously edema-free.¹⁵ Edema may be produced even in healthy persons by the administration of large quantities of salt, followed by the drinking of copious amounts of water.¹⁶ Moderately increased plasma chloride values were obtained on 2 of our 7 patients at the time of the onset of the edema, and at albumin levels of 2.89 and 2.23 gm. One patient (Chart 1) had received 6 gm. of sodium chloride daily for 4 days prior to the appearance of generalized edema and its continued daily intake thereafter for 6 days was accompanied by an intensification of the edema and persistently increased plasma chloride values. Omission of the sodium chloride was followed by a fall in plasma chloride values to normal, accompanied by a rise in serum albumin to 3.2 gm. and a rapid disappearance of the edema over a 6-day period. The second patient (Chart 2) developed an increase in plasma chlorides from 104.1 to 108.6 milliequivalents per liter, despite the fact that no additional sodium chloride was administered during malaria. This was associated with the appearance of dependent edema and puffiness of the hands and face, but to a less marked degree than in the former patient. The edema disappeared after 14 days during which time albumin rose to 3.7 gm., but plasma chloride values remained approximately the same. Though the edema of therapeutic malaria is accompanied by chloride (*i. e.*, sodium) retention, the latter is only a contributing and not the important factor in its production. Increased plasma chloride values occur in patients with suppression of urine, yet edema does not occur.¹⁶ Our findings indicate that sodium chloride intake should be limited during therapeutic malaria, since large amounts may hasten the appearance of edema at a time when plasma albumin and colloid osmotic pressure are reduced. Nevertheless even though sodium chloride intake is limited, edema may still occur.

An additional important factor to be considered is the possible production of an hydremia due to increased sodium chloride intake. Were this so, serum protein values would diminish as a result of the increased blood plasma volume and hydrostatic pressure within

although in 1 case they were first seen on the day after a hemorrhage from peptic ulcer. Coincident with their appearance there is a transitory decreased fragility of the erythrocytes; the latter phenomenon is well known. The following case illustrates the course of events:

Case Abstract. CASE 1.—A woman, aged 23, lost considerable blood during and following the delivery of her second child. On the second postpartum day her erythrocyte count was 3.4 million, her hemoglobin 67% (Sahli). Color index 0.98. There were no target cells, the stained smear appeared normal. The next day a few polychromatophilic erythrocytes were present and some of these were target cells. On the fourth and fifth postpartum days polychromatophilic cells were more numerous (between 1% and 2%) and nearly every one was a target cell. None of the normally stained cells were target forms. In the next few days the number of polychromatophilic cells diminished, as did the target cells and a few target forms were seen in acidophilic cells. The important point is that *at one stage only those cells showed the target form which by their polychromatophilia indicated their recent formation in response to the blood loss.* By the time of the patient's discharge from the hospital on the twelfth postpartum day the erythrocyte count was 4.1 million, hemoglobin 76%, color index 0.92. The stained smear appeared normal; there were no polychromatophilic cells and no target cells.

In most cases, target cells are seen only after a moderately severe hemorrhage. Occasionally the loss of blood is slight, as the following case illustrates.

CASE 2.—A woman received a laceration of the scalp in an automobile accident. Bleeding was, according to her, profuse, but it was stopped in about 45 minutes. No blood count was made until the fourth day later, when it was found to be 4.5 million; 2% of the erythrocytes were target cells. Three days later target cells had disappeared although the erythrocyte count had not changed.

Target cells are usually of normal diameter. In the stained smear they are made up of a rim of hemoglobin-containing material and a central hemoglobin-containing area, the two areas being separated by a zone which is clear, unstained. Barrett conjectured that this appearance was due to a central knob-like projection in a cup or bowl-shaped cell, and showed that a body of such shape would look like a target when viewed on the broad surface. That this is actually the shape of the cell can be seen by oblique illumination of dry smears²⁶ or in bas-relief photographs (Fig. 1). Variations from the typical target form are seen in every smear which exhibits the characteristic appearance. The central stained mass may be joined to the outer rim by a bar of varying thickness; or a ridge may cross the center of the cell, with a thickened central dot. These variations are probably the result both of viewing the dimpled, cup-shaped cell from varying angles and of differences in the distortion of the individual cell.

No target cells are seen in wet preparations. Instead, a number of cells, equivalent to the proportion which appear as target cells

THE SIGNIFICANCE OF TARGET CELLS IN ANEMIA.

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IN 1937 Haden and Evans¹ described what they termed "dimpled" cells in the stained blood smear. The following year Barrett¹ described these cells more fully and showed that when in the circulating blood the cells were bowl-shaped; that in the process of drying they formed a hump in the center, giving rise to what he appropriately named "target" cells. He also discovered that the target cells are very resistant to hypotonic salt solutions *in vitro* and noted their occurrence in anemias associated with obstructive jaundice and in severe hypochromic anemia. Haden and Evans had observed them in small numbers in various anemias but in large numbers in sickle-cell anemia.

Their increased resistance (decreased fragility) in hypotonic solutions has been confirmed by Dameshek,³ who found target cells in Cooley's anemia, and by me. In my case^{2a} increased resistance was exhibited also to acetic acid, so that a leukocyte count could not be made until the acetic acid of the diluting fluid was increased to 3%.

The nature of the target cell has not yet been elucidated and in the light of Dameshek's paper is likely to be disputed. Dameshek reported an anemia resembling Cooley's anemia with as many as 32% of the erythrocytes target cells, which he designated as a "target cell" anemia, though he also found them in other anemias. He regards the target cell as a congenitally defective cell, possibly the fundamental defect in Cooley's anemia, and points out that a cell which is hyperresistant *in vitro* may be hyporesistant *in vivo*. Certain observations of my own, however, incline me to the view that the target cell is a newly formed cell, produced by the bone marrow in response to blood loss regardless of the cause.

In the first place, the appearance of target cells in the stained blood film, far from being an unusual event, is *very common*. Such cells can be found in small numbers, up to 1% or 2%, *early* in the majority of cases of anemia. Rare ones may even sometimes be seen in apparently "normal" smears. In more chronic anemias the number is variable but they may be found in from 1% to 10% or more in many cases.

The presence of the target cells in stained smears is transitory in acute anemia. Often they disappear before there is a significant rise of the erythrocyte count, in this way resembling the reticulocyte. On several occasions they have been present for only 1 or 2 days. Rarely are they present for as much as a week, while in the majority of cases they are seen for 4 or 5 days. They usually first appear on the third or fourth day following a hemorrhage.

blood stream early in the regeneration of erythrocytes and has practically disappeared by the time the red blood count is well on its way to normal. In chronic recurrent blood destruction, as in congenital hemolytic anemia, the reticulocyte counts may be persistently elevated. It is perhaps significant that in Dameshek's "target-cell anemia" there was an increased number of reticulocytes, and that the only one of the patient's relations who showed target cells also had a reticulocytosis.

The one stumbling block to the ready acceptance of this simple concept of the target cell is the oddity of the shape of the cell. Why should the regeneration of blood be associated with a change of shape of the erythrocyte? With one assumption, namely, that the cell does *not* change its shape *in vivo*, it is possible to explain the appearance of the target cell. This assumption is not as startling as may at first sight appear.

The shape of the *circulating* erythrocyte is unknown. While the majority of authors accept the biconcave disc seen on slides as the normal shape of the cell, there have long been dissenters to this view. Weidenreich⁷ was perhaps the first to state that the normal form of the erythrocyte was a "bell-form," basing his claim upon the observation of cells in the mesentery. Radasch⁶ examined sections of placenta and also noted a bowl or bell form, and he supposed that the biconcave form was due to contact of the cells with the air. Repeatedly, bowl-shaped cells have been noted in wet smears of apparently normal blood and in sections of normal tissues. Maximow and Bloom⁵ summarize the status of this question: "Although the fresh human erythrocytes are one of the most common objects of microscopic study, the question of their natural form in living conditions in the circulating blood is still unsettled. Some investigators claim that in reality they are not biconcave discs, but thick-walled, shallow cups, that is, convex-concave discs, and that the biconcave form is merely the result of shrinkage due to an increase in the osmotic pressure of the plasma during examination. It is possible that in the normal blood both forms, as well as all transitions between them, exist at the same time."

I have repeatedly noted cup-shaped cells in histologic sections of blood clots, most of the time in the center of the clot, where presumably there was no contact with the air. It is a simple matter to collect blood with little or no contact with the air, but it is not so simple to achieve the examination of a sufficiently thin film under the microscope without allowing contact with air. Some preliminary experiments along these lines have demonstrated the presence of significant numbers of bowl-shaped cells in normal blood, and these experiments are now being continued.

If the bowl-shaped cell is the normal form of the erythrocyte, the biconcave disc is the result of the deforming influence of the atmo-

in the stained smear, appear as shallow or, more uncommonly, deep bowls or cups. Rarely, the bowl shape is preserved in the dry smear (upper part of Fig. 1). When blood is diluted with hypotonic salt solutions of varying concentrations the proportion of bowl-shaped cells (or of target cells in dry smears) increases as the salt concentration decreases. This is due to the hemolysis of the normal appearing cells and the preservation of the target cells. Even in distilled water a few target cells may resist hemolysis, and most of them resist hemolysis in 0.3% NaCl. The target cells are resistant to acetic acid in concentrations which destroy normal cells.^{2a}

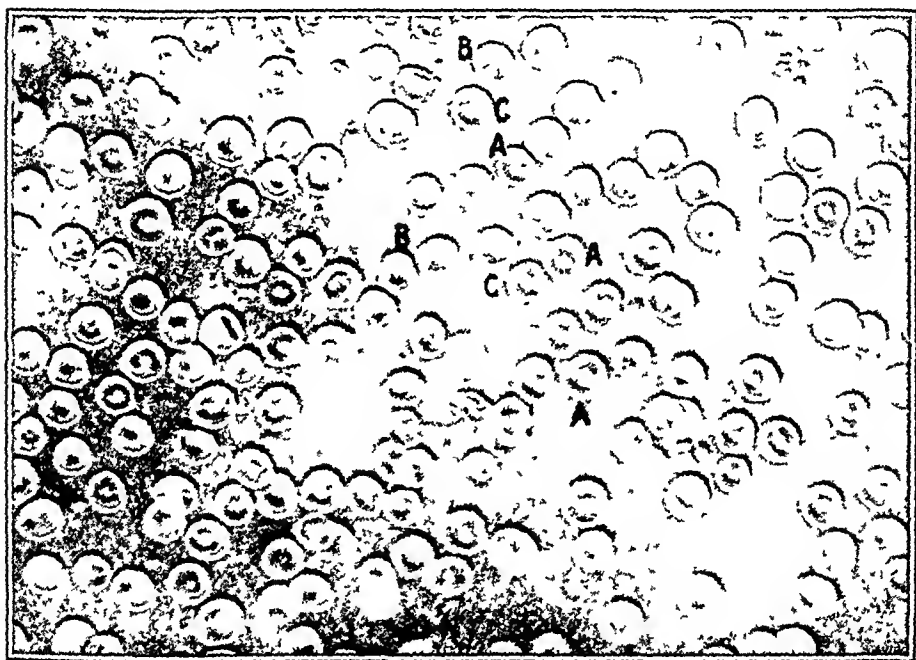


FIG. 1.—Bas-relief photomicrograph of target cells, made by printing through superimposed positive and negative films. Cover-slip dry smear, Wright stain. Some target cells, marked A; a bowl-shaped cell, marked B; an intermediate stage, C. Cells which maintain their bowl shape in dry smears are of rare occurrence.

There seems to be little reason for assuming that the target cell is a fundamentally deficient cell in any type of anemia. Certainly neither the frequency of occurrence nor the number of such cells in Cooley's anemia is any greater than they are in sickle-cell anemia or in cases of acute blood loss. The common occurrence of target cells, if watched for, in the early phases of regeneration of blood does not indicate that this cell is congenitally malformed in the same sense as the sickle cell, the elliptical cell, or the spherocyte. The target cell is merely a hyperresistant young cell which appears in the blood following loss of blood. If the loss is chronic the cells may be present constantly and in large numbers. Its occurrence is analogous to that of the reticulocyte, which also appears in the

hemolytic action of hypotonic saline and to acetic acid has been demonstrated.

5. The contention that the target cell represents the fundamental defect in Cooley's anemia seems to be unjustified. It is simpler, in the light of available evidence, to regard the target cell in this disease, as in sickle-cell anemia and many other anemias, as a response to the blood destruction rather than the cause of it.

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TWO CASES OF STAPHYLOCOCCIC MENINGITIS TREATED WITH ASPARAGIN BACTERIOPHAGE.

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RECOVERIES from meningitis in which the *Staph. aureus* is the offending organism are sufficiently uncommon to suggest that the therapeutic agent employed in a successful case may have been responsible for the favorable outcome. Survival of patients with this highly fatal lesion has been reported following the use of various procedures and combinations of therapeutic agents. Up to February, 1941, there had been reported in the American and British literature 15 such recoveries. The treatments used in these cases were as follows:

Case 1: Repeated transfusions of blood and surgical drainage of the cisterna magna.³

Case 2: Sulfanilamide by mouth.³

Case 3: Sulfapyridine by mouth.⁷

Case 4: Repeated lumbar punctures, cisternal tap, blood transfusions, intravenous fluids, staphylococcus antitoxin intravenously and intrathecally, and sulfanilamide intrathecally and by mouth.¹⁴

Case 5: Staphylococcus antitoxin intrathecally, intramuscularly, and "Prontosil" intramuscularly.⁶

Case 6: Lumbar puncture, blood transfusions, antimeningococcus serum, and sulfanilamide.⁵

sphere.* A change in shape of the cell after it is removed from the body is not a new concept. The sickle cell is not sickle shaped within the blood stream but becomes so when exposed to increased carbon dioxide tension. There is reason to suppose^{2c} that the eccentricity of the elliptical cell increases after removal from the body. In line with this assumption, the target cell is one which resists the action of the atmosphere toward biconcavity and maintains a modification of its normal intravascular shape. Its increased resistance to the atmosphere is correlated with its increased resistance to the hemolytic action of hypotonic solutions and to acetic acid.

It should be pointed out that, however valuable these increased resistances may be for the recognition or isolation of the target cells, the functional value of the hyperresistant cells must lie in some other form of increased resistance not yet recognized. The normal cell within the body is not exposed to the atmosphere, nor to solutions of markedly lowered osmotic pressure, nor to acids. Its reactions are the opposite of those of the spherocyte. The laboratory examination of this latter cell utilizes its diminished resistance to hypotonic salt solutions, but it is merely an indication and not the property of the cell which is responsible for the increased hemolysis *in vivo*; for the blood in congenital hemolytic anemia, or in any other known condition, never reaches the degree of hypotonicity which would hemolyze the abnormal cells.

No evidence has yet been presented to support the contention³ that the target cell, hyperresistant *in vitro*, is *in vivo* more friable than the usual erythrocyte, and that the destruction of such cells leads to a hemolytic anemia, Cooley's anemia. Until such evidence is forthcoming, it is simpler to conceive of these cells as produced following the increased destruction of blood. In Cooley's anemia the cause of this destruction is as yet unknown, and no fundamental defect of the erythrocyte can yet be said to have been demonstrated.

Conclusions. 1. Target cells are commonly seen in the regeneration of blood, regardless of the cause of the blood loss.

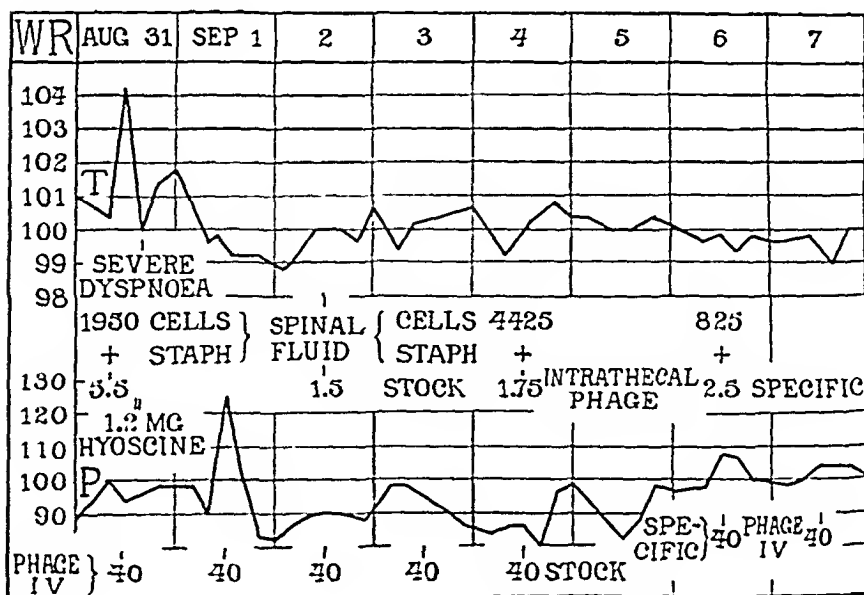
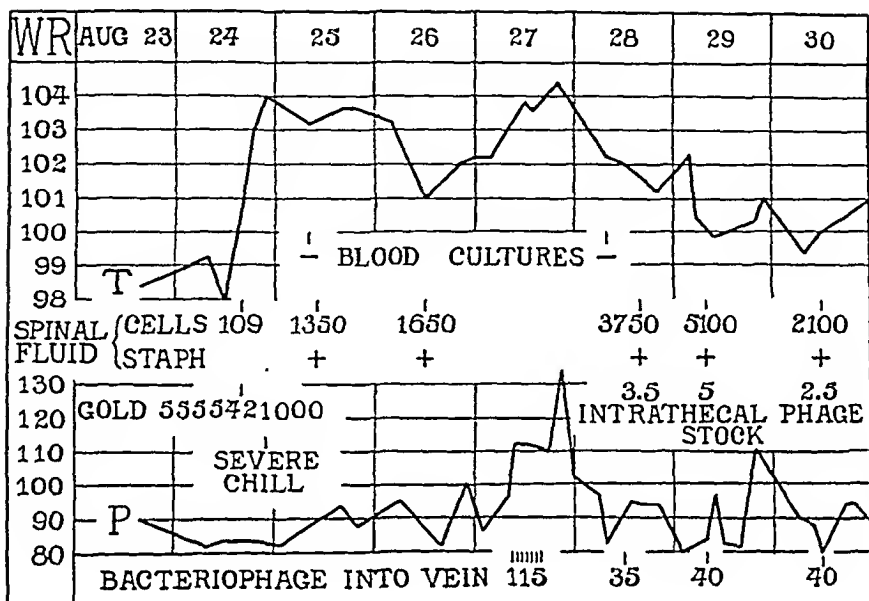
2. In acute anemias they are present for only a short time early in the regenerative phase, and they have disappeared by the time a significant rise of erythrocyte count is evident. In chronic anemias they may be present over long periods of time.

3. The question of the normal shape of the circulating erythrocyte should be reexamined. It is possible, but not yet proven, that the target cell preserves the bowl shape of the intravascular cell in modified form and resists deforming influences which are responsible for producing the biconcave disc seen in blood outside the body.

4. The target cell is a hyperresistant cell produced by the bone marrow in response to the blood loss. Increased resistance to the

* The word atmosphere is here used very loosely to include all those influences which may affect the blood cells once they are removed from the body.

asparagin bacteriophage* and to add the recovery of one of them to the list of 15 already recorded.



* The bacteriophage used in the treatment of these patients was supplied by the Department of Bacteriology of the New York Post-Graduate Medical School and Hospital, Columbia University, New York City.

Case 7: Intraventricular gentian violet.⁹

Case 8: Intravenous gentian violet.²

Case 9: General supportive measures. No "specific" treatment.¹

Case 10: Antimeningococcus serum intrathecally, antistreptococcus serum plus 1:4000 dilution of acriflavine intrathecally, 5 cc. of commercial bacteriophage preparation plus 1:4000 acriflavine intrathecally, and (following isolation of the specific organism) 5 cc. of commercial bacteriophage intrathecally at 24-hour intervals for four doses.⁴

Case 11: Broth bacteriophage intrathecally.¹⁷

Case 12: Broth bacteriophage intrathecally.¹⁷

Case 13: Sulfanilamide, blood transfusions, and repeated lumbar punctures.¹²

Case 14: Broth bacteriophage intrathecally.¹⁶

Case 15: Sulfathiazole intravenously, subcutaneously, by mouth, and intrathecally.¹⁵

In order to gain additional insight into this problem the records of all patients with bacteriologically proven *Staph. aureus* meningitis seen at this hospital from 1925 through 1940 were reviewed. Of these, there were 17. One patient who received massive doses of staphylococcus antitoxin (320,000 units), and sulfapyridine by mouth until the blood level reached 8 mg. per 100 cc., was discharged as cured, but personal investigation by one of us (D. B. F.) discovered that this patient suffered a relapse at home and succumbed to the infection.

During this study there was discovered a large group of patients on whom the diagnosis of "purulent meningitis" had been made but bacteriologic proof of the exact etiologic factor had not been obtained. In these cases culture of the cerebrospinal fluid either was not performed or showed no growth. In all cases, however, the spinal fluid was described as "purulent" and the clinical syndrome did not suggest luetic, tuberculous or "sterile" meningitis. These cases were also studied because of the possibility that in some of them the staphylococcus might have been the infecting organism. In this group there were 81 patients of whom one survived. This was a 16-month-old infant with an infected myelomeningocele whose spinal fluid contained "excessive numbers" of leukocytes. Bacteriologic examination was not performed. Following surgical excision of the myelomeningocele recovery was prompt.

The mortality rate, therefore, in the 17 cases of bacteriologically proven staphylococcic meningitis was 100%, and in the "purulent" group was 98.7%. From the fact that only 15 recorded recoveries could be readily found in the English literature we believe that it may be safely assumed that the general mortality rate from staphylococcic meningitis does not vary to any great extent from the above figures. It is our purpose here, therefore, to describe the treatment of 2 patients suffering from this disease by means of

that there existed a small pustule about 5 cm. from the site chosen for insertion of the needle. The fluid removed at this time showed 109 lymphocytes per c.mm. and a gold sol curve of 5555421000. Within 4 hours following this procedure the patient suffered a shaking chill with rise of temperature to 104° F. Lumbar puncture the following morning (Aug. 25) revealed 1350 cells per c.mm., nearly all of which were neutrophils. At this time it was noted that nuchal rigidity and Kernig's sign were present. Culture of the fluid taken at this time revealed, 36 hours later, a profuse growth of *Staph. aureus*. Before the bacteriologic report was available sulfanilamide was begun by mouth, 1 gm. every 4 hours. This was administered on Aug. 26 and 27. When the bacteriologic examination revealed that the noxious microbe was the staphylococcus, bacteriophage therapy was begun at once and the sulfanilamide discontinued. Because of the possibility of a concurrent septicemia, a blood culture was taken and intravenous bacteriophage begun at the same time according to a dosage schedule previously outlined.¹⁰ Thus, on Aug. 28, 115 cc. were given intravenously in divided doses and 14 cc. of the 1:4 dilution with 0.4% saline were administered intrathecally (3.5 cc. of actual bacteriophage). On Aug. 29, and subsequent days until Sept. 4, 20 cc. were given intravenously morning and afternoon. Larger doses were not employed because the blood remained sterile. The intrathecal dose varied from day to day, depending in part on how much of the spinal fluid could be withdrawn; in general, about two-thirds of the amount of fluid removed was replaced with the hypotonic dilution of bacteriophage. Thus the patient received intrathecal doses of 1:4 dilution in the amounts of 20 cc. on Aug. 29, 10 cc. on the 30th, 22 cc. on the 31st. None was given on Sept. 1, but the patient received 6 cc. on the 2d, 7 cc. on the 4th, and 10 cc. on the 6th. On Sept. 1 rather large doses of hyoscine were given in an effort to control acute mania and this was followed by marked reduction in respiratory rate, fall in blood pressure, and deep cyanosis. However, he rallied from this "low." On Sept. 8th he received 12 cc. intrathecally; on the 11th, 17 cc.; on the 13th, 14 cc.; on the 15th, 12 cc.; and on the 17th his final intrathecal injection of 10 cc.

Laboratory findings revealed negative blood cultures on Aug. 25 and 28. Cultures of the spinal fluid revealed pure growth of *Staph. aureus* on Aug. 25, 26 and 30. No growth occurred on specimens obtained on Sept. 2, 14 and 20. Stained smears of the spinal fluid revealed Gram-positive cocci in clumps on Aug. 25, 26, 28, 29, 30, 31, and on Sept. 4, 6 and 8. No organisms could be seen on Sept. 11, 13 or 15. The patient was discharged from the hospital as cured 30 days after his original admission.

This patient had been admitted originally with the intention of administering malarial hyperpyrexia as treatment for the luetic involvement of the central nervous system. It is interesting to note that 2 months after his bout of fever due to the meningitis he returned to the hospital feeling well and 20 pounds heavier than he had been previously. Malarial therapy was subsequently administered without mishap. The clinical course of the meningitis is outlined in the accompanying chart.

CASE 2.—R. T. (Univ. of Michigan Hosp. No. 270059), a 20-year-old white male, had first been seen here in July of 1931 at the age of 11, suffering from acute osteomyelitis of the femur. Over the next 8 years, despite repeated surgical intervention, the process spread to involve the left femur, right metatarsals, right ulna, left radius, right femur, both mastoid areas, left tibia, right humerus, left metatarsals, left fibula and tibia, left humerus, and the left knee. Each of these areas had been treated surgically on at least one occasion. Cultures of the pus from each site had shown pure growth of *Staph. aureus*. Throughout this period repeated blood cultures had always been negative.

In the selection of a therapeutic agent to be used in the treatment of these patients we followed the advice of Josephine Neal: "In cases of meningitis due to the Staphylococcus . . . bacteriophage should be used if available."¹³ The bacteriophage used was prepared in asparagin medium suitable for intravenous injection according to techniques previously described by others.¹¹ It was given in full strength into the vein but for intrathecal injection was diluted 1:4 with 0.4% saline solution in order that the resulting solution might be hypotonic.

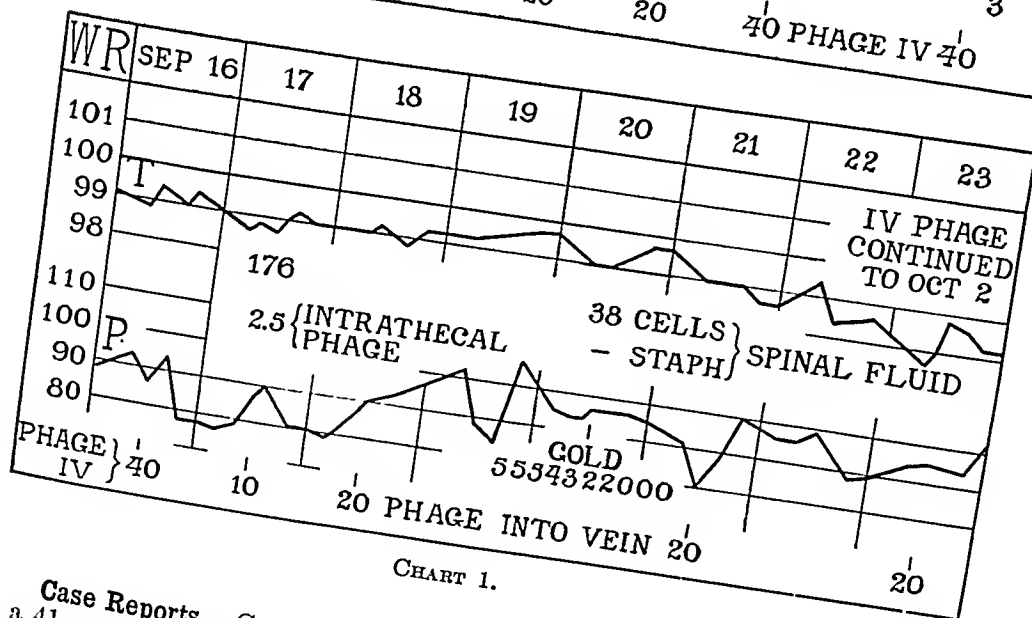
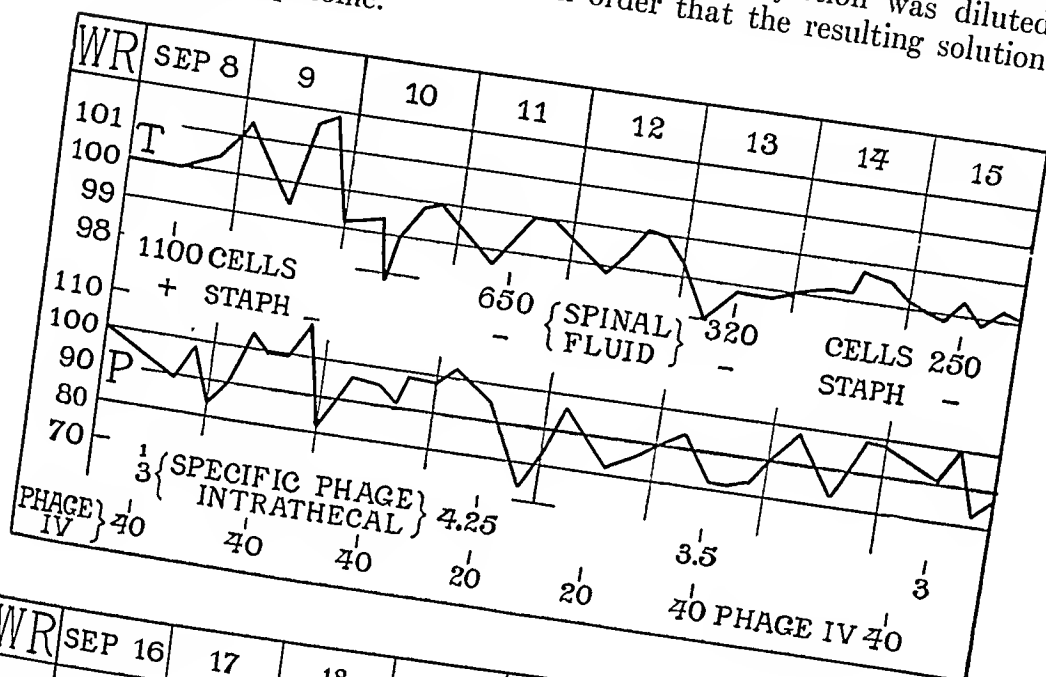


CHART 1.

Case Reports. CASE 1.—W. R. (Univ. of Michigan Hosp. No. 448868), a 41-year-old white male, was admitted to the ward with the diagnosis of syphilis of the central nervous system on Aug. 23, 1939. The following day, Aug. 24, a diagnostic lumbar puncture was performed despite the fact

NOTE ON LOCALIZED LIPOID ATROPHY IN DIABETES.

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NUMEROUS cases of localized fat atrophy at the site of insulin injections in diabetic individuals have been described by various authors since the first cases were reported by Barborka¹ and Depisch¹ in 1926. The atrophy is usually first observed about 3 months after insulin administration is instituted, although it may appear later. The great majority of the cases reported in the literature have occurred in women and children, the lesion being quite rare in adult males. In a diabetes clinic with an enrollment averaging about 300 patients, we have seen only 2 cases of fat atrophy in a period of 4 years, 1 in a young girl and the other in an adult female.

The etiology of this condition remains obscure, although many theories have been proposed by the various authors who have reported cases. However, disappearance of the atrophy has been reported by several authors. Chapman² observed disappearance of the lesion in a patient 2½ years after omitting insulin entirely. Nichols³ reports regeneration of fat during a period of 3 years after changing the site of injections. The general conclusion of all authors, regardless of etiologic theories, was that repeated injections in a localized area should be avoided in order to prevent the occurrence of fat atrophy following insulin administration. That recovery may take place without variation of the site of injection is demonstrated by one of the cases which came under our observation.

Case Report. L. G., female, age 10 years, was first admitted to this hospital on January 26, 1938, in acidosis. She recovered after the usual treatment and was discharged 16 days after admission on a diet of 60 gm. protein, 200 gm. carbohydrate, and 50 gm. fat. A single dose of 40 units of protamine zinc insulin in the morning sufficed to control the glycosuria satisfactorily throughout the day.

Due to poor coöperation at home and to the somewhat subnormal mentality of the patient, the prescribed diet was not followed closely and, as a result, the patient had frequent periods of marked glycosuria. The addition of a dose of regular insulin did not improve the degree of control obtained. Following her return from a private diabetic camp in August, 1938, approximately 7 months after insulin was first administered, fat atrophy over both upper arms was first observed (Fig. 1). She had had no swelling, redness or pain at the site of injections in the arms at any time. Her mother was advised to transfer the site of injections to the thigh which had not been used heretofore.

On Sept. 22, 1939, the left ulna was incised and drained because of further extension of the osteomyelitic process. The evening of that day he developed left facial palsy of the peripheral type. On October 2 the left ear began to drain and paracentesis of this drum was performed in an effort to improve drainage. On October 6 definite signs of meningitis developed and on the following day a radical mastoidectomy was performed on the left side. Because all previous cultures from wounds had yielded *Staph. aureus* it was thought likely that the meningitis was due to this same organism and treatment was begun with asparagin bacteriophage in divided doses intravenously¹⁰ on the day of the mastoidectomy (Oct. 7), the patient receiving a total of 50 cc. on this date. Lumbar puncture was postponed to the following day, due to the inability of the patient to cooperate. On Oct. 8, therefore, he received 17 cc. of the hypotonic solution intrathecally. With but slight variation this dose was repeated daily through Oct. 16, the day of the patient's death. In addition, he received 20 cc. morning and night by the intravenous route. The initial culture of the spinal fluid taken on Oct. 6 showed pure growth of *Staph. aureus*. On Oct. 10 a report was received that the fluid drawn the day before contained not only the staphylococcus but also many colonies of *Strep. viridans*. Because of this fact and the realization that bacteriophage was not effective against the streptococcus, sulfapyridine was administered by mouth in doses of 1 gm. every 4 hours from Oct. 10 to Oct. 15. Under this combined therapeutic regimen the spinal fluid became sterile on Oct. 11 and additional cultures obtained on Oct. 12, 13 and 14 revealed no growth. The patient failed to realize this, however, and his course continued downhill until he ceased to breathe on Oct. 16. Postmortem examination was not permitted.

Summary. 1. Recoveries from meningitis due to the *Staph. aureus* are uncommon—the general rate of mortality being in all likelihood between 98% and 100%.

2. Reference is made to 15 cases of this disease followed by survival of the patient, and the treatment employed in each is briefly mentioned.

3. Two cases treated with asparagin bacteriophage intravenously and intrathecally are presented. The recovery of one of these is noted and the treatment outlined in detail.

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associated with growth of the child and with considerable normal fat deposition elsewhere, as noted in the photograph. During this period of 1 year the patient gained over 10 pounds in weight.

Certain significant problems present themselves when one considers the etiology of subcutaneous fat atrophy following the injection of insulin. If the sole cause of the atrophy is the repeated injection of insulin in one area, the rarity of the lesion is certainly remarkable.

It is quite safe to surmise that especially in the average outpatient department, where patients who disregard instructions are not uncommon, there are many diabetics who inject their insulin within the confines of a relatively small area. Yet, Rosenberg and Berliner⁷ observed fat atrophy in only 32 out of 4000 diabetics receiving insulin, an incidence of less than 1%. It is highly probable that such factors as inflammation or cell injury are not the sole factors involved, since these undoubtedly occur after the injection of substances other than insulin. That the presence of diabetes is not essential to the occurrence of atrophy after insulin injection is demonstrated by a case described by Blotner² in which insulin injections were administered to a non-diabetic in the treatment of undernutrition. Fat atrophy identical in appearance to that occurring in diabetics after insulin administration developed in this patient.

It appears quite likely that some intrinsic factor in certain patients makes them susceptible to this condition and that when this factor is eliminated, spontaneous recovery occurs. Joslin⁵ states that the condition occurs exceptionally in patients whose diabetes is controlled. It is quite probable that this plays a significant part (as in the present case), but in view of the rarity of this condition among diabetics including those poorly controlled and its occurrence in non-diabetics, another factor in fat metabolism undoubtedly plays an important rôle.

Conclusion. Although repeated injection of insulin within a restricted area is not advisable on general principles, this case appears to indicate that recovery from localized fat atrophy may occur in spite of continued injection of insulin in and around the involved area.

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On August 24, 1938, the patient was hospitalized in mild ketosis which rapidly cleared up under treatment. At this time she was receiving 1 dose of protamine zinc insulin and 2 doses of regular insulin in her thighs. The atrophy in the arms had shown slight progress.

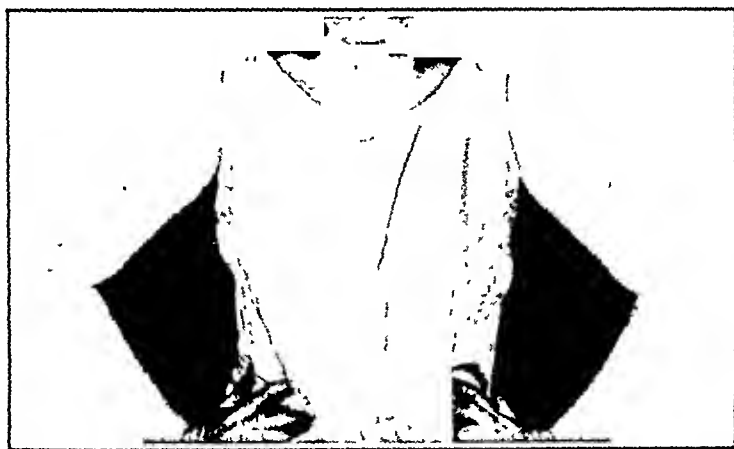


FIG. 1.—Marked lipid atrophy (7 months after first administration of insulin).

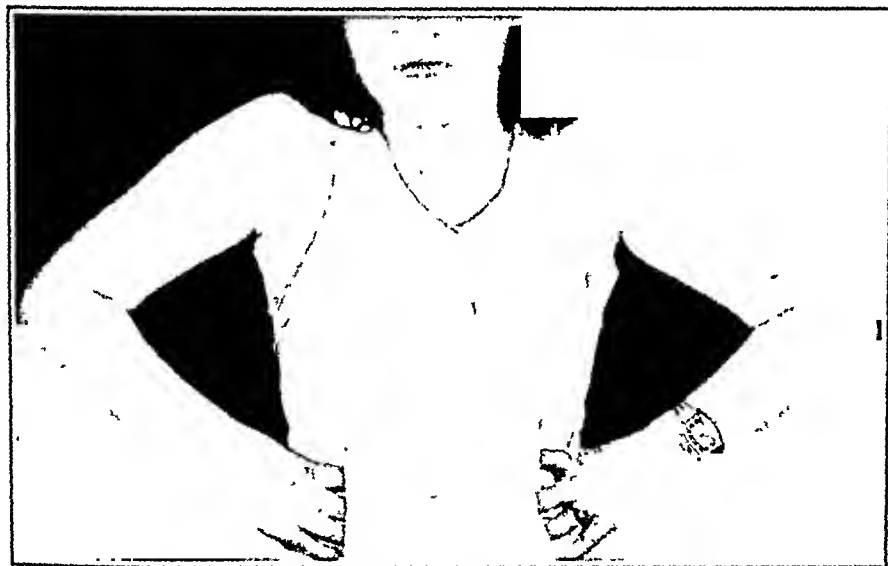


FIG. 2.—Recovery from localized fat atrophy in spite of continued injection of insulin in and around the involved area.

Fat atrophy in both thighs was first observed on May 17, 1939. The condition of the upper arms had shown no improvement at this time but had continued to progress although no insulin was being given in the arms at this time. It was decided to continue injections in the thighs and arms in order to determine if recovery would occur even though injections were continued in and around the areas of atrophy. During the following year the degree of control of diabetes in this case improved considerably, although not to the extent of being entirely satisfactory for any prolonged period of time. Nevertheless, gradual and complete restoration of subcutaneous fat in both arms and thighs occurred. The appearance of the arms on June 26, 1940, is illustrated in Figure 2. This restoration of subcutaneous fat was

CARDIAC CLINICS. A Mayo Clinic Monograph. By FREDRICK A. WILLIUS, B.S., M.D., M.S., in Med., Head of Section of Cardiology, Mayo Clinic, and Professor of Medicine, Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester, Minn. Pp. 276; 35 figures. St. Louis: The C. V. Mosby Company, 1941. Price, \$4.00.

ACCORDING to the author's foreword: "These brief informal discussions appeared without special order of subject matter in the Proceedings of the Staff Meetings of the Mayo Clinic. . . . The guiding idea was a desire to present concise practical discussions dealing with the heart, intended primarily for the busy general practitioner of medicine, who usually is accorded little consideration by medical authors. It was on this account that all the discussions were brief; each could be read in less than ten minutes, and this brevity has been maintained."

The Reviewer agrees that the general practitioner can find much interesting information in this little book.

W. J.

STRANGE MALADY. The Story of Allergy. By WARREN T. VAUGHAN, M.D. Pp. 268; 38 illustrations. New York: Doubleday, Doran & Company, 1941. Price, \$3.00.

THIS is the second in a series of non-technical books sponsored by the American Association for the Advancement of Science and addressed to the intelligent lay public. The Association is to be doubly congratulated, both on the choice of subject and the choice of the author. It is a conservative estimate that a third of all people experience allergy in themselves or their relatives. The recognition and especially the treatment of the manifestations of allergy therefore depend to a considerable extent upon the intelligent coöperation of the patient and his family. The author brings to his task not only a profound knowledge of his subject but the happy faculty to present in a vivid, fascinating and lucid manner the complexities of theory that clutter this field. Thus the abstractions of the side-chain theory, of immunity, and of anaphylaxis are made clear and understandable to everyone. Physicians as well as laymen will find this book valuable as well as interesting reading.

R. K.

HANDBOOK OF COMMUNICABLE DISEASES. By FRANKLIN H. TOP, A.B., M.D., M.P.H., Director, Division of Communicable Diseases and Epidemiology, Herman Kiefer Hospital and Detroit Department of Health, etc., and Collaborators. Pp. 682; 73 illustrations and 10 color plates. St. Louis: The C. V. Mosby Company, 1941. Price, \$7.50.

THE purpose of this book is to furnish practical information for all persons whose professional duties necessitate contact with certain communicable diseases. Thus it will prove to be a handy text not only for students, practitioners of medicine, and nurses, but also for lay personnel in health departments. The first section deals with general considerations applicable to communicable diseases, with chapters on infection and immunity, epidemiology, regulations governing control of communicable diseases, specific prevention, serum and serum reactions, management of communicable diseases in the home, in the hospital. The second section is devoted to the individual diseases, classified by common portal of entry. The third section includes tables epitomizing the contagious disease experience in the Herman Kiefer Hospital over a 10-year period, including complications and diagnostic problems; a table listing the case, contact, and dwelling status of reportable infectious diseases under the laws of Detroit; a glossary of nearly 400 medical terms. While not sufficiently detailed to serve as a general work of reference, the book is entirely adequate for prac-

BOOK REVIEWS AND NOTICES

ELIMINATION DIETS AND THE PATIENT'S ALLERGIES. A Handbook of Allergy. By ALBERT H. ROWE, M.D., Lecturer in Medicine, University of California Medical School, San Francisco, California; Consultant in Allergic Diseases, Alameda County Hospital, Oakland, California. Pp. 264. Philadelphia: Lea & Febiger, 1941. Price, \$3.00.

ELIMINATION diets have proved a valuable aid in the diagnosis and treatment of food allergy. As their leading exponent, the author of this volume presents yet further improvements in their application, based on a wider experience and accumulated knowledge. Important modifications include a fruit-free diet, a cereal-free diet, diets without cottonseed oil and shortening, elimination diets for diabetics, for the young, the obese and the undernourished. Detailed instructions are given, including sample menus and recipes. In addition there are chapters on the diagnosis of allergy in general, its manifestations and its control, furnishing an adequate clinical survey of the subject. In the appendix is much practical information, including questionnaires and history forms for eliciting the history in cases of allergy; food diary forms; directions for the administration of pollen antigens; a botanical classification of edible plants; a list of the ingredients of many commercial foods; the vitamin content of foods; and many recipes. The chief characteristic of the book is its highly practical clinical approach, which should recommend it both to practitioners and allergists. R. K.

THEORY OF OCCUPATIONAL THERAPY FOR STUDENTS AND NURSES. By NORAH A. HAWORTH, M.A. (CANTAB.), M.R.C.S., L.R.C.P., D.P.M., Late Senior Assistant Medical Officer, Severalls Mental Hospital, Colchester, and Honorary Assistant Physician, Lady Chichester Hospital for Functional Nervous Diseases, Hove, and E. MARY MACDONALD, Principal, Dorset House School of Occupational Therapy, and Occupational Therapist in Charge of the Allendale Curative Workshop, Bristol, with a Foreword by SIR ROBERT STANTON WOODS, M.D., F.R.C.P., Consultant Adviser in Physical Medicine to the Ministry of Health, etc. Pp. 132; 81 illustrations. Baltimore: The Williams & Wilkins Company, 1941. Price, \$2.00.

AN elementary and concise statement of the uses and methods of application of occupational therapy, this book was written for nurses and for students of the subject, but it would prove instructive and stimulating reading for many physicians. Psychiatrists and orthopedists have of course long known the therapeutic value of productive activity, but many internists, surgeons and other members of the staffs of general hospitals give too little thought to this therapeutic measure, and would do well to obtain an orderly viewpoint of the subject by browsing through this little volume. It discusses occupational therapy in the treatment of mental disorders, in mental nursing, in the treatment of tuberculosis and cardiac disease, in the treatment of surgical and orthopedic cases; and considers the problems of finance, equipment, stocking, storage and use of waste materials in occupational therapy. There are appended drawings and descriptions of suitable apparatus; lists of suppliers (British) of materials and apparatus; and a considerable bibliography of all aspects of the subject. R. K.

Journal of Technical Methods and Bulletin of the International Association of Medical Museums, No. XXI, October, 1941. Editorial Board: ROBERT A. MOORE, Editor, J. LUDWIG ASCHOFF, J. EARLE ASH, WILLIAM BOYD, VIRGIL H. CORNELL, TRACY B. MALLORY, MATTHEW J. STEWART, CARL V. WELLER. Pp. 88; illustrated. Toronto: International Association of Medical Museums, 1941.

The Symposium in this number on the use of x-rays in pathology is of especial interest. The single article on congenital cardiac malformations reminds one of the prominent part that this journal has taken in the past in presenting the English-speaking literature on this subject. It is to be hoped that with Dr. Abbott's death this feature will not be lost. E. K.

Epilepsy and Cerebral Localization. A Study of the Mechanism Treatment and Prevention of Epileptic Seizures. By WILDER PENFIELD, Litt. B., M.D. (Johns Hopkins), D.Sc. (Oxon., Princeton), Professor of Neurology and Neurosurgery, McGill University; Director of the Montreal Neurological Institute, and THEODORE C. ERICKSON, M.A., M.Sc., M.D. (Minnesota), Ph.D. (McGill), Associate Professor of Surgery, University of Wisconsin. Chapter XII by HERBERT H. JASPER; Chapter XX by M. R. HARROWER-ERICKSON. Pp. 623; 163 illustrations. Springfield, Ill.: Charles C Thomas, 1941. Price, \$8.00.

Teaching Preventive Medicine to Medical Students. With Special Reference to the Use of Health Department Facilities. By HUGH R. LEAVELL, M.D., Dr. P. H. Pp. 77. New York: The Commonwealth Fund, 1941.

Strange Malady. The Story of Allergy. By WARREN T. VAUGHAN, M.D. Pp. 268; 38 illustrations. New York: Doubleday, Doran & Company, 1941. Price, \$3.00. (Review, p. 884.)

NEW EDITIONS.

Practical Methods in Biochemistry. By FREDERICK C. KOCH, Frank P. Hixon Distinguished Service Professor of Biochemistry, University of Chicago. Pp. 314; illustrated. Third Edition, revised. Baltimore: The Williams & Wilkins Company, 1941. Price \$2.25

In this edition new methods for uric, lactic and pyruvic acids have been added. Except for typographical corrections, no other changes have been made in this excellent laboratory manual. D. W.

Diseases of the Blood and Atlas of Hematology. With Clinical and Hematologic Descriptions of the Blood Diseases Including a Section on Technique and Terminology. By ROY R. KRACKE, M.D., Professor of Bacteriology, Pathology and Laboratory Diagnosis, Emory University School of Medicine; Pathologist to the Emory University Hospital, etc. Pp. 692; 46 text illustrations and 54 color plates. Second Edition, thoroughly revised, reset and enlarged. Philadelphia: J. B. Lippincott Company, 1941. Price, \$15.00.

The Modern Treatment of Syphilis. By JOSEPH EARLE MOORE, M.D., Associate Professor of Medicine, The Johns Hopkins University; Physician-in-charge Syphilis Division of the Medical Clinic and Visiting Physician, The Johns Hopkins Hospital, etc. With the Collaboration of JAROLD E. KEMP, M.D., Associate in Venereal Diseases, The Johns Hopkins University; HARRY EAGLE, M.D., Passed Assistant Surgeon, United States Public Health Service and Lecturer in Medicine, The Johns Hopkins University; PAUL PADGET, M.D., Associate in Medicine, The Johns Hopkins University, and MARY STEWART GOODWIN, M.D., Instructor in Pediatrics, The Johns Hopkins University. Pp. 674; 98 illustrations. Second Edition. Springfield, Ill.: Charles C Thomas, 1941. Price, \$7.00.

tical purposes. The general level of excellence is of a high order. Features worthy of separate mention are: the general discussions of control and prophylaxis; the chapters on management of communicable diseases in the home and in hospital (written by nurses); the tables on communicable disease statistics from the Herman Kiefer Hospital; the many excellent illustrations. In a few instances the description of specific prophylaxis is not sufficiently detailed. The book should find a wide appeal. R. K.

 NEW BOOKS.

William Henry Welch and the Heroic Age of American Medicine. By SIMON FLEXNER, and JAMES THOMAS FLEXNER. Pp. 539; illustrated. New York: The Viking Press, 1941. Price, \$3.75.

A Manual of the Treatment of Fractures. By JOHN A. CALDWELL, M.D., Professor of Clinical Surgery, College of Medicine, University of Cincinnati; Director of the Fracture Service, Cincinnati General Hospital, Cincinnati. Pp. 150; 76 illustrations. Baltimore: Charles C Thomas, 1941. Price, \$3.50.

Hippocratic Medicine. Its Spirit and Method. By WILLIAM ARTHUR HEIDEL. Pp. 149. New York: Columbia University Press, 1941. Price, \$2.00.

Lectures on War Neuroses. By T. A. ROSS, M.D., F.R.C.P. Pp. 116. Baltimore: The Williams & Wilkins Company, 1941. Price, \$2.00.

Immunization to Typhoid Fever. (The American Journal of Hygiene Monographic Series, No. 17, September, 1941.) From the Research Laboratories of the Army Medical School, Washington, D. C. Supported by the De Lamar Fund of The Johns Hopkins University. Pp. 276; illustrated. Baltimore: The Johns Hopkins Press, 1941. Price, \$2.50.

An X-Ray Atlas of Silicosis. By ARTHUR J. AMOR, M.D. (Lond.), M.Sc. (Wales), Honorary Physician, Clydach Memorial Hospital; Medical Officer, Mond Nickel Company, Ltd., Swansea. With Translation of the Legends into French by ROBERT E. HORNE, M.A. (Wales), Medical Secretary, Mond Nickel Company, Ltd., Swansea. With a Foreword by SIR WILSON JAMESON, M.A., M.D. (Aberdeen), F.R.C.P., of the Middle Temple, Barrister-at-Law; Dean of the London School of Hygiene and Tropical Medicine. Pp. 206; 6 text illustrations and 72 plates. Baltimore: The Williams & Wilkins Company, 1941. Price, \$8.00.

Shock Treatment in Psychiatry: A Manual. By LUCIE JESSNER, M.D., Ph.D., Resident Psychiatrist, Baldpate, Georgetown, Mass.; Graduate Assistant in Psychiatry, Massachusetts General Hospital; Assistant in Psychiatry, Beth Israel Hospital, Boston, and V. GERARD RYAN, M.D., Associate Psychiatrist, Elmcrest Manor, Portland, Conn.; Assistant in Psychiatry, Harvard Medical School. Introduction by HARRY C. SOLOMON, M.D., Clinical Professor of Psychiatry, Harvard Medical School; Chief of Therapeutic Research, Boston Psychopathic Hospital. Pp. 149. New York: Grune & Stratton, Inc., 1941. Price, \$3.50.

Pathology of the Oral Cavity. By LESTER RICHARD CAHN, D.D.S., Associate Professor of Dentistry (Oral Pathology), Columbia University, etc. Pp. 240; 165 illustrations. Baltimore: The Williams & Wilkins Company, 1941. Price, \$5.50.

The Premature Infant. Its Medical and Nursing Care. By JULIUS H. HESS, M.D., Professor and Head of the Department of Pediatrics, University of Illinois College of Medicine; Attending Pediatrician, Illinois Research and Educational Hospital, Cook County and Michael Reese Hospitals, and EVELYN C. LUNDEEN, R.N., Supervisor, Premature Infant Station, Sarah Morris Hospital, Chicago. Pp. 309; 63 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, \$3.50.

size of hemoglobin. Of all the viruses known to attack the human nervous system, the virus of poliomyelitis has the most limited host range. The virus, as contained in human tissue or excreta, has previously been found to be pathogenic only for certain monkeys and chimpanzees but not for mice, guinea pigs or rabbits but reports of new hosts are included later in this review. Poliomyelitis virus possesses highly specialized tissue affinities. From numerous studies it has been found that poliomyelitis virus never multiplies in cells other than the neurons of susceptible hosts. Sabin summarized the course of events in human poliomyelitis on the basis of present knowledge as follows: "It seems to me that one may be permitted to visualize the virus entering the human body by way of the mouth and establishing itself throughout the alimentary tract, where it proceeds to multiply. While further work is necessary to indicate to what extent various levels of the alimentary tract are affected, there is already more than suggestive evidence that the walls of the pharynx and small intestine are among the chief sites of virus multiplication, and the feces, the chief means of virus elimination. Whether the virus multiplies in the nerve cells, which are contained in the walls of the alimentary tract, or in the non-nervous tissues remains unknown. However, whatever the type of cells affected in the alimentary tract, the virus may be visualized as beginning its invasion of the central nervous system essentially along two pathways: one leading into the medulla by way of the cranial nerves that supply the upper part of the tract or by way of the parasympathetic system along the vagus from the lower part, and the other leading into the spinal cord either along the visceral afferent fibers through the spinal ganglions or along the efferent fibers from the intestine by way of the abdominal sympathetic ganglions. If the greater attack and spread of the virus is along the first pathway one may expect a syndrome in which bulbar signs are primary, while if the second pathway is more predominately affected the primary paralysis would be in the extremities. That these pathways perhaps may be used simultaneously, the outcome depending on the route by which the virus arrives in the central nervous system first, is suggested by the fact that in a purely bulbar case the virus has been found in the pharynx, ileum, colon and abdominal sympathetic ganglions. The inapparent or abortive type of case would be either one in which virus multiplication is limited to the alimentary tract or one in which the virus also invades the central nervous system but fails to destroy a sufficient number of cells to give rise to clinical signs. This view is based in part on the recent finding in monkeys inoculated with human virus that an equilibrium may be reached between the host and the virus before sufficient neurons have been destroyed to interfere with apparently normal function. Similarly, in the non-paralytic type of poliomyelitis, the virus may be visualized as multiplying in the alimentary tract and invading the central nervous system, but the activity of the virus is suppressed before a sufficient number of neurons to give rise to paralysis has been destroyed. That the virus may continue to multiply in the alimentary tract long after the disappearance of clinical signs of the disease is evident from the fact that in some instances the virus has been found excreted in the stools for weeks and months after clinical recovery. . . ."

The foregoing theory of the means or portal of entry of the virus of

PROGRESS OF MEDICAL SCIENCE

PEDIATRICS.

UNDER THE CHARGE OF
ALVIN E. SIEGEL, M.D.,
MACON, GEORGIA.

POLIOMYELITIS—A SURVEY OF RECENT CONTRIBUTIONS.

IN this department in January, 1934, the then recent literature of poliomyelitis was reviewed. Since that time there have been one or more epidemics of this disease each summer with result that many contributions to the subject have appeared. These have included clinical and case reports, statistical studies, as well as reports of investigative study. The sum total of this literature is a mountainous mass of articles, but boiled down to a concrete basis very little has been added to our knowledge of this disease.

Our interest in this disease has been reawakened this year by the epidemic especially in the southeastern section of this country, which began in the early summer in several cities of Florida and insidiously spread to neighboring states. A great deal of interest has been developed from the epidemiologic viewpoint because of the very large concentrations of young men in the military service in the South, as well as because of the fact that these soldiers have been further concentrated in certain areas on maneuvers to which have been added thousands of troops from posts in the North. It is not possible so early to determine to what extent the young men in the army have contracted the disease and to what degree extension of the areas of epidemic has occurred by the return of military units from epidemic areas to their home stations where epidemic had not prevailed.

According to Sabin²⁸ poliomyelitis is an acute infectious disease that is caused by a filtrable virus with sufficiently distinct properties to permit its identification with as much certainty as is possible to identify any of the well-known bacteria. The etiologic agent of poliomyelitis is known to be one of the smallest filtrable viruses. It can pass through the finest filters and membranes, which retain not only the bacteria but most viruses as well. It can be sedimented only by prolonged centrifugation on powerful ultracentrifuges and it is known that the individual virus particle is large enough to accommodate only a few molecules the

Swan,³³ examining the central nervous system of 8 patients with poliomyelitis by routine neurohistologic methods, found that 4 of these cases showed an absence of changes in the olfactory bulbs. He believed that infection by the virus of poliomyelitis by the olfactory route is either less common than has been thought or it is less fatal. Because the most intense changes were seen in the tissues forming the floor of the fourth ventricle, which extends through the whole length of the brain stem and below is continuous with anterior intersegmental tract of the spinal cord, this median longitudinal bundle must be considered as an important path for the spread of the pathologic process.

Studies of the stools of individuals suffering from poliomyelitis have revealed the presence of the virus. Toomey³⁴ has demonstrated that the virus of anterior poliomyelitis can be recovered from the stools of human beings ill with the disease. It has also been proved that the virus is present in sewage in areas where the disease is prevalent. Toomey is of the opinion that the virus of poliomyelitis enters the human system by way of the gastro-intestinal tract and that there is no support for the theory of nasal passage as even an occasional port of entry of the disease.

Kramer³⁵ reported a study from children in a separate wing of a small institution comprising 20 infants and children of preschool age. Of this group, 5 contracted poliomyelitis with fatal results in 1 child and non-paralytic results in 4 children. In 3 additional children there was evidence of fever of from 24 to 48 hours' duration. The virus of poliomyelitis was recovered from the stools of 3 of the 12 remaining healthy children, from contacts of children having the disease and from 2 of the 3 children who had fever but for whom the diagnosis of poliomyelitis was not established. In all, 10 of the 20 children harbored the virus of poliomyelitis sometime during the 30-day period of observation.

While the presence of the virus of the disease in the stools seems indisputable, that another factor is present in the stools of patients ill with poliomyelitis is suggested by Toomey and Takacs.³⁶ They commented that stasis of the intestine occurs frequently in patients with poliomyelitis. The toxic factor present in their stools may be due to the increase of bacterial virulence of resident organisms. The effect of the bacteria present in the stool did not seem important, since a sterile fecal eluate was just as toxic as the whole stool. These experiments suggested to the authors that convalescent poliomyelitis serum may have the ability to neutralize not only poliomyelitis virus but also a toxic factor present in the gastro-intestinal tract. That this is not improbable was seen from the fact that the agglutinin titer against enteric organisms rose as the experimental animal with poliomyelitis became better.

The virus has been demonstrated in the stools by a number of observers besides those quoted. The presence of the additional toxic factor, as suggested by the work of Toomey and Takacs, has not caused the publication of confirmatory or contradictory opinions some 6 months after the appearance of their paper. It may be that such will appear after sufficient time has elapsed. Little or no sponsorship of the nasal or olfactory port of entry is found in the literature of the past 4 years. Therefore, until disproved by new evidence, the alimentary tract should be accepted as the portal of entry.

this disease into human body exemplifies the trend of thought on the subject. Until recently the nasopharynx was thought to be the portal of entry, and different chemical agents were recommended for spraying into the nasopharynx as a means of prevention against the disease. Commenting on the port of entry as a result of very recent contributions, an Editorial^{7b} observes that many factors point to the alimentary tract as a locus of virus proliferation. In many instances the material suggests that the spinal cord is the primary site of the invasion of the central nervous system. It has not been possible to determine the exact pathway of the virus from the intestine to the central nervous system except that the vagus nerve has been strongly suspected. There has also been evidence that the nerves supplying the pharynx were the path of entry. There is evidence that there may be many ports of entry and that the olfactory route is of little importance in man.

Zahorsky³⁷ stated that the theory that the nasal route is the portal of entry of the virus of poliomyelitis was not convincing. He thought that the gastro-intestinal tract might be the portal of entry, and that the contamination of fresh fruits and other foods, milk products and water by flies and their excreta was worthy of consideration. He pointed out that while across the river from St. Louis poliomyelitis was endemic for a number of years, there were only isolated cases of the disease in St. Louis. This reference is of interest as Zahorsky suggested an alimentary portal of entry at a time when it seemed definitely established that the nasopharynx and the olfactory system were culpable. The general opinion at this time is strongly in favor of the entrance of the disease into humans by way of the alimentary tract although there are some who still have not been convinced that the olfactory theory of entrance has been disproved. Sabin and Ward²⁹ revalued the prevailing hypotheses of the disease in human beings. The absence of demonstrable virus in the olfactory bulbs and anterior perforated substance indicated that in man the olfactory pathway need not be affected. The absence of infective virus in the nasal mucosa suggested that this is not the site of virus multiplication and dissemination. The virus was not present in the salivary glands, which indicated that the saliva is not an elimination route. The positive results with the tonsils and pharyngeal mucosa were probably due to the pharyngeal tissue rather than to the tonsils. In the alimentary tract the virus was present not only in the content but also in the washed walls of various parts of the tract, including the pharynx, the ileum and occasionally the colon. They thought that infection of the alimentary tract was the result neither of primary localization nor of portal of entry. The distribution in the central nervous system was found to be limited to certain areas, and it was not as indiscriminately disseminated as viruses such as equine encephalomyelitis which can invade through the blood-vessels or those such as rabies which are capable of extensive centrifugal spread. The pattern of virus distribution in human poliomyelitis, according to this study, pointed to almost the entire alimentary tract as the primary site of attack by the virus and no support was found for the concepts involving either the olfactory or the respiratory systems. The distribution also militated against the cutaneous route although it may be conceivable that occasional infection through the broken skin may be possible.

and Frauchiger and Messerli¹³ were interested in paralysis in other domestic animals. They described observations on 2 hogs which presented symptoms that greatly resembled those of acute anterior poliomyelitis. On this basis such a diagnosis was made and both animals were killed. Study of the spinal cords revealed histologic aspects resembling those of acute poliomyelitis in human subjects. Material from the spinal cords of these animals was introduced into two hogs and into one steer. Because of inadequate technique, nothing could be learned from the inoculation test on the hogs; but the steer, in which a formerly devised technique was employed for the inoculation, developed fever of a "dromedary" (camel) type. Other symptoms included signs of fatigue, stiffness of the neck and an ataxic walk. From the seventh day after the inoculation the symptoms commenced to subside and a few days later the animal seemed normal again. The animal was killed 14 days after the inoculation. The histologic findings of the central nervous system were those of a lymphocytic meningo-encephalomyelitis rather than those characteristic for poliomyelitis. However, it was possible that had the animal been killed during the acute stage of the disease lesions more typical of poliomyelitis might have been found. Because of Spielmeier's demonstration that similar histologic aspects do not necessarily indicate the same disease, etiology or causal agent, the authors did not definitely conclude that the described paralytic symptoms in hogs were identical with human poliomyelitis, but they did believe that this could be the case.

In Burnet's⁴ epidemiologic experiments the most important results indicated that infection did not produce poliomyelitis antibody, that certain children with initial antibody nevertheless suffered from paralytic infection and that cynomolgus monkeys could be infected with the local virus by ingestion or by pharyngeal swabbing. As regards age incidence, he was led to the conclusion that an important change in the character of the disease had taken place in the last 30 or 40 years. It would seem that in the earlier period poliomyelitis was essentially an adult infection with incidental involvement of infants, while now epidemic poliomyelitis is a disease of childhood, and spread by child contact.

Aycock² made observation on 1004 patients or photographs of patients with various crippling conditions to test the clinical impression that paralytic poliomyelitis exhibits a tendency to selective occurrence in certain types of individuals. The significant proportion of correct readings obtained confirmed this impression and verified Draper's concept of a "poliomyelitis type," as well as anthropometric studies indicating a difference in bodily measurements from the normal. There was additional evidence to support the epidemiologic observation that the frank disease tends to occur in but a limited and selected fraction of those exposed. These individuals are possessed of an autarchologic susceptibility as shown by the disease to familial aggregation and that the character in question is a physiologic difference of an endocrine nature, which, although to a large degree subclinical, manifests itself in the clinically discernible characteristics of the individuals. This occurs in a slight degree in younger girls, moderately in younger boys and older girls, and to a still greater degree in boys 10 years of age and older.

Granting that this theory of alimentary transmission is correct, the question naturally arises as to how the infectious material reaches the individual. Inoculation might occur by partaking of foods or fluids that have been contaminated with the infectious material in a manner similar to that in which typhoid fever transmission occurs. Ellsworth⁹ cited the report of Lovett and Richardson who in 1911 reported that, in 419 cases of infantile paralysis observed by them from 1908 to 1910, 105 patients (slightly more than 25%) had swum, waded or paddled in more or less contaminated waters just prior to the attack. Precedent accidents, overexertion and falls were reported in another group of cases. Of these factors overexertion definitely lowers the body resistance and it is conceivable that this may predispose to infection. Not only overexertion but prolonged periods of bathing or swimming, in which the body gets severely chilled, may act in a similar manner.

To Paul and Trask²⁵ it has become increasingly apparent during the past 2 years that the virus of poliomyelitis may be readily isolated from the stools of patients with poliomyelitis. This is true not only in cases of the paralytic type but the virus has also been demonstrated in the stools of patients with the abortive type of the disease. From their study these authors commented that newer methods of testing human feces and sewage have been of assistance in detecting the existence of the virus of poliomyelitis throughout an infected community during epidemic times. River and harbor water and large volumes of sewage were tested in three urban epidemics. The virus of poliomyelitis was detected in two sewers both of which were in the vicinity of hospitals, and from these tests it was learned that not only can the virus content of sewage be large but the virus may be transported for short distances at least in flowing sewage. They believe that poliomyelitis is probably transmitted by a number of different channels. Among these is the direct or indirect factor of close intimate contact between infected persons, illustrated by the type of interfamilial contact in which juvenile members of a family usually share. Many of these infected persons may be convalescent carriers in the first few weeks of their recovery from either a diagnosed or a missed case, and some of the exposed persons may become transient "healthy" carriers. There may be also a variety of other channels, in which contaminated foods, milk and water or possibly insects, mammals or birds, play a part. Watercourses and particularly watercourses polluted with sewage may be one of the channels of transmission.

The fact that difficulties arise in the transmission of poliomyelitis in man to experimental animals has given rise to the general belief that other animals than man and certain species of monkeys are not infectable with the disease. Frauchiger and Hoffman¹² attempted the transmission of the disease to cattle. Poliomyelitis material from human subjects was inoculated into 3 heifers. Large doses were given by the intranasal, intraperitoneal and intraspinal routes. Except for increase in the temperature at the onset, general symptoms, such as gastrointestinal disturbances, nasal discharges and sweating, were absent. There were no signs of meningeal irritation. However, after 2 or 3 days signs of paralysis appeared in the extremities, particularly the posterior. The paralytic symptoms increased until the seventh day, but there was never complete flaccid paralysis. This was a very interesting study

period. It is suggested that the trauma of the operation opens avenues of infection along the nerves of the pharyngeal region to the medullary nuclei. This is, of course, the avenue of infection that for some years was supposed to be the means of entrance of the virus of poliomyelitis into humans. As has been discussed above the alimentary tract has come now to be considered the portal of entry.

Fischer, Stillerman and Marks¹¹ in a very recent publication commented on the increasing interest in the relation of tonsillectomy and adenoidectomy to poliomyelitis. Most of these cases following operation have shown the bulbar form. They studied the records of an epidemic that occurred in Toronto. These records were kept in an excellent manner with especial reference to the history of previous tonsillectomy and the date of the operation. The first part of this study entailed the collection of data on 507 patients with poliomyelitis who were from 3 to 12 years of age at the time of the epidemic. The patients were classified as tonsillectomized and non-tonsillectomized, and the two groups were analyzed according to the month of occurrence, the age at the time of onset, the type of and the mortality from poliomyelitis and the relation of the length of the interval between tonsillectomy and onset of the disease to the type of poliomyelitis. It was found that poliomyelitis took the bulbar form in the largest proportion of those patients in whom the disease developed within 1 month after tonsillectomy. Also the percentage of cases of the bulbar form among the children with poliomyelitis who had a history of tonsillectomy, regardless of when performed, was over twice as high as that in the non-tonsillectomized children with the disease. This difference was in conformity with the statistics on types of poliomyelitis in the series reported by Eley and Flake (*loc. cit.*). In the second part of this study, with the coöperation of public health and school officials, a large sample of the school population was surveyed to obtain information on the general incidence of tonsillectomy. It was shown what was the actual number of school children in the sample who had been tonsillectomized at any time and the date of the operation in each case. From these data it was possible to compute the incidence of poliomyelitis during this epidemic among recently tonsillectomized children. This part of their study showed a higher incidence of poliomyelitis in the recently tonsillectomized group than among other children, but since the total number of cases of poliomyelitis in the tonsillectomized group was only 8, a number too small to give a statistically significant difference, the result by itself cannot be considered conclusive. The frequent reports in late years of the occurrence of poliomyelitis in recently tonsillectomized children does give some confidence in the significance of the reported study. They pointed out that on epidemiologic grounds alone there would not be expected a higher incidence of poliomyelitis among recently tonsillectomized children than among other children, because other things being equal, there is no reason to expect any difference between the degrees of exposure of the two groups. If anything, the recently tonsillectomized children seemed to be less exposed, so far as they were isolated from other children during the period of operation and convalescence. The higher incidence of poliomyelitis among the recently tonsillectomized children suggested a lowered resistance to the disease. The mechanism of this lowered resistance

In Dauer's⁵ study of 231 cases of poliomyelitis in children under 13 years of age, from 90% to 95% had some paralysis, and the remainder had, besides the clinical symptoms, an increase of cells in the spinal fluid. From the standpoint of geographic location, there was evidence that there may be some form of direct or indirect contact between patients or a common source of infection or both. In 2 instances the disease appeared in 2 members of the same family; in 2 instances it appeared in 2 persons in the same institution; in 2 instances it developed in different families in the same dwelling, and in 3 instances the disease was reported from adjoining houses.

Helms and Willcocks¹⁷ in their report commented on the meteorologic factors in relation to the increased incidence of cases. Commencing in spring, the cases attained a maximum in midsummer and then gradually declined. A somewhat similar correlation was suggested in the incidence of seasonal rainfall in northern parts of New South Wales. In the metropolitan area, during early weeks of the epidemic and while the weekly incidence was increasing, severe paralysis developed in a greater proportion of patients than during the later stages of the epidemic. In rural districts this tendency may have been masked by the fact that a relatively small population is spread over a large area. The number of deaths was greater in the rural districts at the beginning and at the height of the epidemic than in the later stages. In the metropolitan area there appeared to be a tendency for the age group up to 4 years to be proportionately smaller at the beginning of the epidemic than in its later stages. This tendency may have been masked in the rural districts for the same reason that the severity of the paralysis was masked. Among other factors they discussed the relation of tonsil and adenoid operations in the occurrence of poliomyelitis. Of 711 patients 7 were known to have had a tonsillectomy and adenoidectomy from 7 to 22 days prior to the onset of the illness. Bulbar and spinal paralysis developed in 3 of these 7 patients, 2 had paralysis of the palate, 1 had spinal paralysis with no evidence of bulbar involvement and 1 patient had the non-paralytic form of the disease. There were no deaths.

Eley and Flake⁸ stated that the fact that a bulbar form of acute anterior poliomyelitis had been reported as following recent tonsillectomy and adenoidectomy has suggested that this procedure may in some manner influence the entrance of the virus. They studied 418 consecutive patients with poliomyelitis. There were 287 patients with spinal poliomyelitis, and in 8 of these the disease occurred within 30 days after the removal of the tonsils and adenoids. In only 3 of these did the disease develop within 7 to 18 days after the operation. Of 131 patients with bulbar poliomyelitis, 17 had this operation performed within 20 days prior to the onset of their illness. In 15 of these 17 patients the disease developed within the incubation period of from 17 to 18 days.

Koskoff, Amshel and Lebeau²² reported 2 cases of bulbar poliomyelitis following tonsillectomy and adenoidectomy. They stated that, although their patients may have developed the disease without the operation, this did not seem likely. The patients were both well preoperatively. The onset of the disease falls well within the experimental incubation

results secured with mice appeared to be more trustworthy than those usually secured with monkeys, as mice are more uniformly susceptible. The results agreed with those obtained with human serum in monkeys. These considerations should render it possible to follow serum immunity in population groups from different localities and from infancy to adulthood and thus ultimately clarify many epidemiologic questions awaiting solution.

Barber³ reported 4 cases of anterior poliomyelitis occurring on the same day in a boys' school. Since no other cases developed in this school, a close analysis was made of the daily habits and lives of these boys. Cases did appear later in the village and 2 of them occurred in the family of one of the maids employed by and living in the same house of the school in which the 4 boys lived. These cases were attributed to the maid carrying the infection home. As she was in the house for the rest of the term and no further cases occurred there, and as one attempt to infect a monkey from her proved negative, there was no actual evidence that she was a carrier. The house in which the 4 boys lived had separate feeding arrangements and a separate domestic staff from the rest of the school. Only 2 of the boys slept in the same dormitory. The other 2 were in different dormitories, and each was unconnected with the others in any activity. In the house-room all 4 boys were in different corners and 1 of them was present only occasionally as prefect. In the school all 4 were well scattered, being in different classes and other categories. The only common factors appeared to be the same feeding arrangements and contact with the domestic staff. The only connection with food was that strawberries, obtained from 2 farms, 1 of which had been affected, were served only in the house where the affected boys lived. The simultaneous onset certainly resembled a food-poisoning outbreak rather than an epidemic spread by droplet infection.

Until now there has been no definite or generally accepted idea of the transmission of poliomyelitis. It would seem that the theory of the alimentary tract as the portal of entry would furnish the best explanation of the rather small incidence of the disease in relation to the population even in epidemics. It has been thought that many escape the infection because of having developed immunity. Such has been the idea in reference to adults. However, although frequent small infections with the causative factor may give rise to the immunity that most adults seem to have, sometimes even a definite attack may not give rise to complete immunity, so that second attacks have been recorded. Toomey^{3a} recorded the eighteenth case of a second attack of poliomyelitis. This case was similar to the cases reported by others but it was not felt that it was a bona fide second attack. The objection was based on the theory that a person who has had poliomyelitis is a prey not so much to another attack of the same disease as to other diseases, such as influenza, measles and scarlet fever, which involve the few remaining peripheral nerve fibers and their cells of origin. Toomey felt that the subsequent paralysis in his case were the result of influenza affecting the remaining nerves and cells. It could have been toxic neuritis in a person who had an old poliomyelitis. In the presence of any acute infection, such as influenza, bronchopneumonia, measles, coryza due to the virus of the common cold or scarlet fever, or in the

was not altogether clear, but probably it was related either to the portal of entry of the disease or to the avenue of its spread. It was thought that traumatized adenoid and tonsillar tissue may afford the portal of entry for the virus in some cases. One suggestion was that the tonsils and adenoids serve as a barrier. Their removal eliminated this barrier with the result that the virus often gained a foothold.

Numerous recent studies^{7a} on the immunologic reactions of the poliomyelitis virus have resulted in a considerable extension of knowledge of its behavior. Successful adaptation of human poliomyelitis virus to the cotton rat and white mouse is one of the most promising advances in practical research technique of the present decade. Earlier, monkeys were the only susceptible animal species until Armstrong^{1a} reported the transference of rhesus poliomyelitis virus to the eastern cotton rat. The disease thus produced in cotton rats was characterized by flaccid paralysis of the extremities associated with degenerative lesions of the anterior horn cells. These lesions were apparently identical with those usually observed in human poliomyelitis and in experimental poliomyelitis in monkeys. The identity of the rodent infection with rhesus poliomyelitis was further indicated by the fact that the rodent infection would produce typical poliomyelitis symptoms and lesions on return inoculation into monkeys. It was later reported by Armstrong^{1b} that the rhesus virus, once serially adapted to the cotton rat, could be successfully transferred to white mice. Proof of this transference was incomplete because it was found that the mouse virus was non-pathogenic on return inoculation into monkeys. This loss of pathogenicity suggested that the human poliomyelitis virus might have been lost and the observed symptoms in mice might have been due to some unknown neurotropic environmental virus. In order to complete the proof of the successful transference of the human virus to mice, Jungblut and Sanders^{20a, b} studied the antigenic properties of the passage virus directly isolated from the mouse brain and cord or after propagation in mouse tissue culture. Confirming earlier investigators, they found that on serial inoculation into the cotton rat the human virus rapidly lost its pathogenicity for monkeys. Simultaneously with this attenuation for the rhesus monkey there was an increase in rodent pathogenicity. Still further increases were noted in the mouse until a "fixed" virus was eventually obtained, which was wholly non-pathogenic for monkeys. This fixed virus could be successfully transmitted and adapted to mice, by preliminary serial passage through monkeys and cotton rats. The most encouraging results have been the claimed successful immunization of monkeys by the repeated subcutaneous injections with living mouse virus. This specifically attenuated viable murine vaccine is readily grown in artificial tissue cultures. While the immunity conferred by this viable vaccine is not absolute, it is sufficiently effective to stimulate the hope that better results will follow further clinical research. If this vaccine does ultimately prove effective, Armstrong's original observations may become one of the major discoveries of modern research medicine.

Haas and Armstrong,¹⁶ in the mouse protection test, using 83 human sera and the Lansing strain of poliomyelitis virus, found that serum antibodies capable of neutralizing the Lansing strain of poliomyelitis virus were widely prevalent especially among older individuals. The

protein increase and this becomes more marked with the progress of the disease. Globulin is always found, although it may be only a trace. The Lange gold curve often affords useful corroborative evidence.

Hunt¹⁸ stated that the changes in the spinal fluid varied with the stage of the disease and with the reaction of the meninges. In the systemic phase the fluid usually increased in amount, the cell count was from 30 to 100 per c.mm., and the aggregate of cells was made up entirely of neutrophils or of both leukocytes and lymphocytes. The globulin was increased in some cases and not in others. In the stages of paralysis the fluid was still increased in amount, the number of cells varied from 18 to 2000 or more and from 80 % to 90 % of the cells were lymphocytes. In general, the highest cell counts were shown by the patients showing symptoms of severe meningeal irritation. In the fatal cases the cell counts of the spinal fluid were invariably high, averaging above 200 cells.

Meyer²⁴ studied the leukocytic formula in 57 cases of poliomyelitis and also in a varying number of cases of other conditions which might be confused with it. He found that in cases of poliomyelitis during the period of invasion and the first days of paralysis there is a slight leukocytosis, with a slight increase in neutrophils. This gives way little by little to a slight lymphocytosis, with the occasional appearance of rare plasmocytes and a monocyte count of 9 % or more. The eosinophils and basophils tend to disappear. After the establishment of the paralysis, the leukocytic formula returns to normal, or there may be a slight leukopenia. The only other condition which might be confusing from the standpoint of the blood picture was acrodynia, but the gradual onset makes the clinical differentiation easy.

Spector and Hobart³² commented that the most characteristic finding in their series was the resistance of the patient against flexion of the spine. Most of their cases, that did not manifest this sign, were of the bulbar type. The next most common sign was muscle tenderness. In all of their cases the sensorium was clear and the patients were coöperative. A few of the bulbar cases were drowsy, but that was apparently due to dehydration and disappeared upon the adequate administration of fluids.

Gordon, Hudson and Harrison¹⁴ tried to produce active immunity, and to demonstrate the effect of passive immunity in monkeys. To establish active immunity they used crude virus, preparations of virus in gelatin containing aluminum and an eluate and found by the neutralization test that there was no evidence to demonstrate that any one of the three antigens was superior or produced a better immunologic response in monkeys. They injected crude virus and a preparation of virus in gelatin containing aluminum into sheep and thought that they obtained a greater antibody response than might be expected with crude virus alone. They were not able to demonstrate any resistance in animals which had been immunized with antigen made of crude virus or with a preparation of virus in gelatin containing aluminum, injected subcutaneously, for the animals became ill when given the disease by the intranasal route. Passive immunity produced by using large amounts of blood from convalescent and hyperimmunized monkeys failed to protect animals when virus was subsequently introduced intranasally. Yet clinical experience fails to reveal more than one attack

presence of an injury, it is right to question the diagnosis of a second attack of poliomyelitis and to insist that first toxic neuronitis be ruled out. If acute infections do not aggravate the clinical condition of an old poliomyelitis, as has been shown experimentally, few of the reported cases in the literature can qualify as actual instances of a second attack of poliomyelitis.

Faber^{10a} visualized poliomyelitis as a disease due to a progressive invasion of the nervous tissue by a virus which is not only neurotropic but strikingly selective within the nervous tissues. It is capable of producing only transient lesions such as hyperemia and cell infiltration in certain parts of the central nervous system as the upper part of the brain stem, destructive lesions or cell degeneration in only a few areas such as anterior horn cells and motor cells of the medulla and slight lesions or none at all in other areas such as the cerebral cortex and cerebellum. In many instances the virus plants itself for a brief time only as it may invade the olfactory bulbs and sometimes the brain stem and then die out without reaching the vulnerable lower motor neurons. These cases are the abortive and non-paralytic types of poliomyelitis. The symptom complex of the disease shows an order of progression corresponding with the advancing distribution of lesions and may be divided into three phases. The first phase is manifested by fever alone and the lesions are confined to the olfactory bulb. The second phase consists of a symptom complex in which more or less generalized effective, sensory and autonomic phenomena are conspicuous, and the lesions consist mainly of basal encephalitis without involvement of the cord. During the third phase there occur two kinds of symptoms. The first kind are autonomic and sensory phenomena arising in the lateral and posterior horns and dorsal root ganglions. The second kind are localized phenomena arising in the anterior horns.

Toomey^{34c} believes that poliomyelitis virus has but a slight affinity for the exposed axons or peripheral medullated nerves, and that it may be that its spread to the central nervous system is stopped by the myelin contained in the sheath which covers the gray fibers. This would explain why there is not in every case of poliomyelitis involvement of the vagus nerve, which is actually a bundle of well-medullated connector fibers. Although these gray fibers might be partly or completely involved in every case of poliomyelitis, few symptoms of this involvement other than constipation would become manifest clinically. Experiments supported the belief that ordinarily virus of poliomyelitis does not spread along well-myelinated nerves of healthy monkeys but that virus will spread along nerves of vitamin D-deficient monkeys if the virus is simply placed in contact with the postganglionic fibers. It is presumed that in the latter animals the preganglionic medullated nerve fibers going to the adrenal gland are made deficient and consequently more susceptible.

Studying the spinal fluid in an outbreak of poliomyelitis, Drury and Sladden⁶ found that detailed and routine analysis of the spinal fluid was a very valuable procedure in the detection and diagnosis of poliomyelitis and also in polioencephalitis. Where a completely normal spinal fluid is found the diagnosis of the disease is negative. Slight pleocytosis is a constant feature of the disease and there are always a few neutrophils present in the early stages. Usually there is slight

alimentary tract as the means of the virus entering the individual, the use of chemotherapeutic agents in the nasopharynx has no prospect of benefit unless from the nasopharynx it passes into the alimentary system in sufficient quantity to effect blocking of the tissues, if Schlutz's idea of the *modus operandi* of these chemicals as prophylactics is true. This effect of zinc and similar substances has not been substantiated in the observations of recent authors.

Fever therapy has been tried in poliomyelitis. The results have not been promising whatever has been the method of inducing the hyperpyrexia. Kohl²¹ used malaria therapy and a protein preparation obtained from bacilli. He did not observe any convincing effects from artificial fever therapy. Rosenow²⁷ compared the results obtained in the treatment of 221 patients with acute poliomyelitis receiving antistreptococcus serum and the effects of the disease among 116 similar patients living under comparable conditions who did not receive the serum. The initial symptoms were somewhat more severe in the group in which serum was administered than in the control group. The results were contrasted on the basis of mortality and residual paralysis. It was thought that the much lower mortality and lower incidence of residual paralysis of the patients given the serum was directly attributable to the action of the antistreptococcus serum. It was noted that restless, nervous children often fell asleep after the first injection of the serum. Headache and pain in the involved extremity or part were lessened or relieved. The temperature, especially among patients in the preparalytic stages, rapidly fell to normal after an initial transient rise. Progressive paralysis often was apparently arrested. Restoration of muscle function was more rapid among the patients who received the serum.

In summing up a review of the serum therapy and vaccination of poliomyelitis Faber¹⁰⁶ stated: "It may be that success in preventing poliomyelitis will not come from the methods of classic immunology but from some simpler chemical procedure—whether it is the use of hormones or vitamins or something else—that will modify intracellular metabolism so that the natural host cells will no longer be suitable for invasion and multiplication of virus. The conditions that make them suitable are narrowly limited and delicately balanced. The chemical differences in composition of the anterior horn cells, which are susceptible, and those of many other neurons which are not, cannot be very great, and there is reason to suppose that even in the former the implanted virus dies out in many cases by the process which Pette calls autosterilization, without causing death of the cells. It does not appear to be beyond the range of possibility that physicians will some day know the secret of this process and perhaps learn how to control it."

Meyer¹²⁶ found that when cerebrospinal fluid from persons convalescing from poliomyelitis was mixed with the virus prior to inoculation of monkeys it was effective in protecting them from the infection. He also treated 13 patients with poliomyelitis with cerebrospinal fluid from convalescents with gratifying results. Because the cerebrospinal fluid is easier to obtain and because it is as effective as the serum, if not more so, and because the removal of the cerebrospinal fluid from the donor may be of benefit to him, the author felt that this procedure was of great benefit to all concerned.

in the same individual, perhaps because the virus has remained alive but "imprisoned" in the body.

Many therapeutic agents have been tried in the treatment of poliomyelitis. It is not possible to enumerate all of them. Many have failed on more detailed trials. Among these is potassium chlorate. Contat and his coworkers showed very satisfactory results but Gsell¹⁵ concluded that the clinical basis of the potassium chlorate treatment was unsatisfactory, although his experimental observations were not on a sufficient number of animals to warrant definite conclusions. Saucier and Stewart³⁰ performed experiments as nearly as possible like those of Contat, Arthus, Spycher and Debat. They failed to protect or influence favorably the course of the disease in monkeys.

Rhett²⁶ studied the effect of neoprontosil as a prophylactic as well as a therapeutic agent in poliomyelitis. The drug was given to 440 acutely ill children, during an epidemic of poliomyelitis, in approximate dosage of 1 gr. per pound of body weight per day. Of these children only 1 developed paralysis. This was a transient paralysis developing on the fifth day of illness in a child whose mother had not kept up the maintenance dosage of the drug. Symptoms subsided when full dosage was resumed and the paralytic involvement had subsided completely in the 3 weeks' period of quarantine. In 2 other children meningeal symptoms developed on the fifth day of illness and in these also the maintenance dose had not been continued. These symptoms subsided without paralysis with resumption of the full dosage of the drug. He reported also 14 cases of poliomyelitis in which neoprontosil was given in the preparalytic stage. Of these only 1 developed paralysis. In 8 cases, in which a clinical diagnosis of meningeal involvement of poliomyelitis was made, there was subsidence of the condition with neoprontosil medication without paralysis developing. There were 11 cases with paralytic involvement treated during this time by the administration of neoprontosil. Toxic symptoms subsided in this group within 24 to 48 hours, and there was no apparent advance in paralytic involvement after the adequate dosage of the drug was reached and held for 24 to 48 hours. There were no deaths during the acute phase of the disease although there were 2 deaths in the cases included in this series where the condition was fulminating with practically complete involvement of all extremities and respiratory musculature, necessitating the use of the respirator. On the other hand, Toomey and Takacs^{35a} concluded from their studies that neither merphenyl borate nor sulfanilamide, in the dosages recommended for clinical use, modifies nor prevents the occurrence of poliomyelitis in monkeys that have been inoculated with the virus of poliomyelitis by way of the intracerebral route. They^{35b} found also that sulfapyridine was of no value in preventing the production of experimental poliomyelitis in monkeys inoculated intracerebrally.

Schlutz³¹ discussed the chemical substances that have been used intranasally in prophylaxis against poliomyelitis. He stated that among the chemicals which have protective qualities zinc sulphate has been found to be most effective. The mode of action, according to this observer, is not known, but he believed that they do not destroy the virus but rather that they modify the permeability of the tissues which serve as portals of entry. In view of the trend of feeling as regards the

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GYNECOLOGY AND OBSTETRICS.

UNDER THE CHARGE OF

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UTERINE FIBROIDS.

ALTHOUGH myomatous tumors of the uterus are the most common tumors of the female generative organs, their exact etiology remains unknown. Almost 10 years ago Witherspoon¹⁹ presented evidence to show that the unopposed action of estrin (the ovarian follicular hormone) in the absence of corpus luteum influence is the cause of hyperplasia of the endometrium. He suggested, moreover, that the unopposed action of estrin on the myometrium, if prolonged sufficiently, would result in fibromyomatous growths. This hypothesis was based on a study of 124 cases of fibroids, diagnosed microscopically and of 26 cases of endometrial hyperplasia diagnosed microscopically, in which a second operation was performed for fibroids some 4 years later. In this latter group the associated ovarian and endometrial findings suggested a cause and effect relationship between ovarian follicular cystic formation, hyperplasia of the endometrium and fibromyomata of the uterus. Witherspoon advanced the hypothesis that the unopposed action of estrin on the uterus results in immediate endometrial change characterized by hyperplasia, and secondly, in more latent myometrial changes in the nature of fibromatous growths.

Within the past year Brewer and Jones³ have presented a study of

Following the use of the mechanical respirator in a case of poliomyelitis that has been widely publicized in the lay press as well as in a number of later cases that gained publicity because of the successful termination of pregnancy in several mothers with respiratory forms of poliomyelitis, this means of maintaining respiratory function in this form of the disease is very well known to the public. During the current epidemic in a number of even small communities in Georgia as well as in some of the larger ones where this equipment was lacking, public subscription has provided the funds to procure respirators. Discussing the use of the respirators Wilson³⁶ believed that confusion exists about the selection of patients with poliomyelitis for treatment in the respirator and that there is a misconception as to the purpose of respirator treatment. He contended that the respirator will aid only when there is a paralysis of the intercostal muscles or of the diaphragm or in rare instances in which there is hypofunction but not dysfunction of the respiratory centers. Unfortunately, most physicians think of the respirator only as a machine for life saving and for aiding the breathing until enough recovery occurs to enable the patient to carry on by himself. The respirator should be considered a device for providing physiologic rest for the muscles of respiration. Too frequently use of the respirator is delayed too long or the patients are taken out of the machine too soon. Most persons are familiar with the respirator which is generally used. Other new types are being developed. One is a room-sized respirator which is able to take care of several persons at a time. This is reported as giving excellent results. Another type is also being developed. It consists of a rigid or semirigid jacket to be put on the chest and abdomen, making an airtight space over the body. The intermittent evacuation of this space by hand or motor-driven pumps causes respiration to be induced in a manner similar to the Drinker apparatus.

The after-treatment of acute poliomyelitis and more especially the treatment of the residual paralysis come under the province of the orthopedist. During the paralytic stage there is little that can be done except to maintain physiologic rest. Under all possible circumstances the orthopedist should be consulted in order that whatever splinting, counteraction or other measures that will minimize the damage to the affected part can be instituted. Irwin¹⁹ pointed out that the treatment carried out during the acute phase was designed to salvage everything of value from wreckage caused by the devastating invasion of the infecting organism. When there is nothing more to salvage the condition passes into the chronic stage. Here the concern should be of adding whatever surgical procedures are indicated and the fitting of permanent braces.

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There was a surprising similarity of symptoms and signs in the two groups. Although some of the myoma group had cardiac damage, he believes that it was not due to the tumor, inasmuch as other exciting disease was present; moreover, similar cardiac damage was present in the control group. No patient died of any cardiac complication despite the presence of coronary artery disease in 3 of them. From this study we may deduce that while the cardiac risk must be taken into account in any operation for myoma, the presence of the myoma, *per se*, does not increase the risk over what it would be for any other major operation.

Irradiation. My former chief, the late Dr. John G. Clark, was one of the American pioneers in the use of radium in the treatment of pelvic disease, and the teachings which he formulated have been followed with slight modification by those who followed him. It will be of interest therefore to review a report by Norris and Behney¹⁵ of 1437 patients treated by radium for benign hemorrhage. We shall concern ourselves with a group of 687 of these cases who had myomas. The important symptom in myoma cases which calls for the use of radium is hemorrhage, but to use an Hibernianism, for those who wish to use radium, the most important thing to know is when not to use it. Norris and Behney list 19 contraindications to the use of radium, which are: 1, When doubt exists as to the accuracy of the diagnosis; 2, the presence of intraperitoneal lesions other than those responsible for the bleeding and which require surgical intervention; 3, rapid growth in the case of a supposed uterine myoma; 4, associated fundal carcinoma; 5, pressure symptoms; 6, softening or other evidence of degeneration; 7, inflammatory lesions within the pelvis, especially those of the adnexa; 8, myoma larger than a 4 months' pregnancy; 9, submucous tumors, especially if pedunculated; 10, myomas in young women; 11, anemia markedly out of proportion to the bleeding; 12, obstructing tumors or malformations that prevent the proper application of radium; 13, radiophobia; 14, the presence of cervical myomas; 15, pregnancy; 16, highly nervous women; 17, previous pelvic operations; 18, painful myomas; 19, myomas after the menopause.

There are good reasons for each one of these contraindications which will occur to the reader with a little reflection, but in some cases exceptions are made; for example, an associated cardiac lesion may make irradiation of a myoma advisable which otherwise would be treated by hysterectomy; or, in an associated fundal carcinoma irradiation may be the method of choice because of extreme obesity or for other special reasons. If it has been decided that the case is a proper one for the use of radium, the dosage should be carefully considered. The efficacy of the remedy in stopping hemorrhage and the ease with which it may be applied constitute definite hazards in this form of therapy, particularly in patients in the child-bearing period. Norris and Behney have made efforts to modify the dosage of radium so that hemorrhage will be checked but without completely sacrificing the ovarian function. Such dosage is less certain and less permanent in its results but they believe that in their earlier cases the dosage employed was too heavy. They found that in patients who received less than 600 mg. hours, the menopausal symptoms were materially less but the results secured were correspondingly diminished. The effect of irradiation in dosages over 600 mg. hours was practically constant both in regard to the percentage

the relationship between the corpus luteum and the endometrium in patients with uterine fibroids in which their conclusions are quite at variance with the above generally accepted hypothesis. They remind us that a close relationship is supposed to exist between ovarian function and the development of fibroids because: 1, fibroids develop only during active ovarian life; 2, they usually cease to grow after the menopause or castration; 3, they grow rapidly during pregnancy; 4, sterility in patients with fibroids is thought to be dependent upon the disturbed ovarian function; 5, abnormal uterine bleeding is a common symptom of patients with fibroids and is often considered to be the result of ovarian dysfunction; 6, cystic glandular hyperplasia has been reported frequently in such patients and since this results from excessive or prolonged estrogenic stimulation, estrin has been considered the common etiologic factor; 7, failure of ovulation has been reported by some observers; 8, the frequent finding of multiple follicular cysts in the ovaries has suggested the possibility of excessive estrin production; 9, endometriosis and adenomyosis are frequent concomitant lesions with uterine fibroids and since these lesions occur only during the active life of the ovaries, the importance of the ovarian hormone as a common etiologic agent is assumed. In spite of all this circumstantial evidence in favor of the estrogenic theory, they decided to study the ovarian function and endometrial relationship in 100 unselected and consecutive patients operated upon for uterine fibroids. They found that ovulation had occurred in these patients similar to that in normal women. Forty-six of the patients had corpora lutea of the present cycle and of these the development of the corpora lutea was normal in 41 as evidenced by histologic study not only of the corpora lutea but also of the endometriums which reflected the characteristic responses to normal corpus luteum hormonal stimulation. Small follicular cysts were present in 21 of the 100 patients but in no instance was there evidence that these cysts had had any influence on the normal physiologic processes of the ovaries or the endometriums, none of them showing hyperplasia. Cystic glandular hyperplasia was present in a moderate degree in only 1 instance in the entire 100 cases, which is at marked variance with the generally accepted view.

From the above discussion it may be seen that we still do not know the reason for the development of fibroids. We have, however, gone a long way in the treatment of this condition since hysterectomy was first undertaken with great trepidation. We know that many fibroids need no treatment whatsoever, but merely observation. Of those that require some therapeutic measures, we may select either irradiation, whether by radium or Roentgen ray, or surgical removal either by myomectomy or hysterectomy, and we shall discuss all of these procedures in turn. In the early days of surgery, an operation was often delayed or proscribed because of the so-called myoma heart. It was believed that the myoma had some toxic influence on the heart which increased the risk of operation. In order to test the validity of this theory Jacobs¹¹ studied, both clinically and electrocardiographically, 30 consecutive patients with proved fibroids, and compared the findings with those of 30 other patients who were operated upon for various pelvic conditions other than fibromyoma. He came to the conclusion that uterine fibromas do not produce any significant changes in the heart.

that injury is possible in the case of early conception, whereas in late conception the ovum would recover completely before it is capable of being fertilized. It has been noted that there is a tendency toward abortion in the first pregnancies following radiation treatment, whereas later pregnancies are more often normal. It seems likely that in many of the early cases abortion is caused by the disease of the uterus or adnexa for which treatment was instituted or by the effect of the radium on the generative organs rather than as the direct effect upon the fetus. It would seem that physicians using radium should make written records warning the patient and her husband against early subsequent pregnancies and that these warnings should be acknowledged in writing. It also seems advisable to interrupt any pregnancy which has been subjected to therapeutic irradiation, for it is generally admitted that serious effects on the offspring will result in a high percentage of cases. These effects are proportional to the amount of radiation and are more serious in early pregnancies, though the fetus may be seriously injured at any stage of development.

Myomectomy. This operation, when it can be applied, is unquestionably the most conservative as it removes the tumors but leaves a functioning uterus behind. Perhaps the strongest advocate of this procedure is Victor Bonney,² of London, who states that women vary in their reactions to hysterectomy; but there is a very definite proportion who take the loss of the womb very much to heart, either because they are aware that to many men the idea of a woman not being "whole" is unattractive, or on account of the irrevocable sterility. Myomectomy has usually had a limited scope, being restricted to cases where the tumors were single, or if multiple, then superficially placed. Resenting this restriction, he has extended the operation until he has been able to perform it in any case if conservation of the uterus is desirable. In a general way his rule is that in patients under 41 years of age the preferential operation is myomectomy, while in patients over that age hysterectomy is desirable, but there are exceptions to the rule. On the one hand is the relatively young woman, who having had sufficient children, wants to have her womb removed, and on the other hand, the elderly woman who, for private reasons, sentimental or otherwise, desires its conservation. He has performed myomectomy 487 times. The fibroids were solitary in 237 cases and multiple in 250 cases. Of the multiple cases, the largest number of tumors he has removed from a single uterus was 125, so it can be seen how far he has extended the indications for the operation. He has had 7 operative deaths (a mortality rate of 1.2%), with no deaths in the last 200 cases. New fibroids have formed in 5% of the cases, but only in 3% to the extent of requiring further operation. All these cases were patients who had developed fibroids at an exceptionally early age and to whom he ascribes a special fibroid-forming tendency. Of 77 women within the child-bearing age who wished and were in a position to have children, 30 (39%) did conceive. Seventy-five per cent of the deliveries were normal and 25% were by Cesarean section. The high percentage of Cesarean operations was due to the relatively advanced age of the mothers and the great obligation to deliver a living child. In speaking of the technique which he employs he lays great emphasis on a special myomectomy clamp which he has invented. This instrument controls both uterine arteries

of menopausal symptoms and satisfactory results. Without going into actual figures, their report shows that in dosages over 600 mg. hours, menopausal symptoms will occur in slightly over one-half of the patients and satisfactory results will be achieved in well over 80%. In order to determine the permanency of their results, they followed 184 patients for 10 years or more and only 4 of them (2%) had recurrences. There were 74 cases which failed to get a satisfactory result from one irradiation; of these a second irradiation relieved 37, hysterectomy relieved 30, myomectomy relieved 2, the remaining 5 being unrelieved. There were 3 deaths in the series, 1 from pneumococcic meningitis on the third day, 1 from cerebral hemorrhage on the fifth day and 1 from intestinal obstruction on the tenth day, an operative mortality of 0.4%.

In presenting an analysis of his series of 986 cases of myoma treated by irradiation Costolow⁵ states that in his opinion some of the contraindications to irradiation are too rigid and patients for this form of therapy are being selected too conservatively. In his experience pre-existing pelvic inflammatory disease is not a justifiable contraindication since acute pelvic inflammation after irradiation occurred in only 1 patient in his series. The average age of his patients was 42.5 years, approximately 75% of the patients being over 40 and therefore, in or near, the menopause. He has found that irradiation menopause is no more troublesome than the normal menopause and furthermore sexual function is not destroyed. In only 4 patients (0.4%) did cancer of the uterus develop after radiation therapy, so that it does not have to be feared in advising such treatment. He states that a remaining uterus is no more likely to become cancerous than a normal uterus in a woman of the cancer age. Inflammatory degeneration of large fibroid tumors occurred in 2 cases, both of which were successfully operated upon at a later date. In tumors the size of a 3 months' pregnancy or smaller (722 cases), there was a reduction of the uterus to normal in 84.3%. Only 2.4% of this group were later operated on. In patients with tumors the size of a 4 months' pregnancy or larger (264 cases) there was a reduction of the uterus to normal in 36.7% and to normal or slightly enlarged (less than twice normal) in 52.7%. Only 4.2% of this group were later operated on. In tumors of this size Roentgen rays alone, preceded by curettage, are the most satisfactory method of radiation therapy in his experience.

In a series of 287 cases of benign uterine tumors Norsworthy¹⁶ found radium to be uniformly satisfactory and while a vaginal discharge persisted for from 3 weeks to several months, it eventually ceased in all cases. The minimum dose he employed was 400 mg. hours; the maximum, 4800 mg. hours, and the series was without mortality.

: While of course radium should not be used in the presence of a pregnancy, it is of interest to know what happens if pregnancy should be present or if the patient should become pregnant after the irradiation. Fortunately no one clinic has had an extensive experience with such situations but the literature has been analyzed by Miller, Corscaden and Harrar¹⁴ who find that the opinion is that pregnancies subsequent to irradiation should be divided into "early" and "late." By "early" is meant conception in the first few months after the application of a temporary sterilizing dose of radium. "Late" conception is that which takes place after the end of the temporary amenorrhea. It is believed

wound cavities, so that special attention must be paid to asepsis during the operation.

The series of 128 myomectomies reported by Miller and Tyrone¹³ represents about 10% of the total number of fibroids treated during the same period at Tulane University in the private service. Where pregnancy was a possibility, about one-third of the cases became pregnant. There was a recurrence of bleeding in 8.5% and only 1 death, an operative mortality of 0.8%. They believe that this low mortality argues very favorably for the safety of myomectomy as compared with hysterectomy, since in this series it was less than one-half that of hysterectomy. They do state, however, that the immediate and remote postoperative complications were of a very serious nature, probably due to faulty operative technique, such as slough of the uterine muscle from tying sutures too tight, or inability to completely cover all raw surfaces. Two cases developed acute intestinal obstruction during their stay in the hospital, both recovering after release of the adhesions which had formed between a loop of ileum and the myomectomy scar. A third patient was 8 months pregnant, following a myomectomy 16 months previously, when the bowel became obstructed in a similar manner, while a fourth patient was operated upon elsewhere for a late obstruction.

After myomectomy at the Mayo Clinic, according to Counseller,⁶⁴ about 35% of the patients became pregnant. He found that recurrences of myomas are more frequent (about 20%) in patients less than 40 and considerably less frequent (8%) in those more than 40 years of age. While he regards the operation as technically more difficult than hysterectomy, the surgical risk is about the same in his experience. A very important point which he mentions is that when a submucous myoma becomes partially or entirely extruded through the cervical canal, the endometrium becomes secondarily infected. It is imperative that these tumors be removed by vaginal myomectomy or approached by vaginal hysterotomy. Should there be associated myomas of the fundus requiring removal, this procedure should be delayed 30 to 60 days until all evidence of infection has subsided.

Hysterectomy. One of the favorite subjects for discussion among gynecologists is the perennial question as to whether a hysterectomy should be complete or subtotal and in a previous review (October, 1937) this question was considered at length. Zondek²⁰ is of the opinion that there need be no discussion of this subject but that supravaginal hysterectomy should be preferred and performed as high as possible in order to preserve a part of the uterine mucosa from which menstruation may take place. If, however, for technical reasons a high amputation cannot be performed, he states that the uterine mucosa should be implanted in the cervix following a low amputation in order to give the uterus the possibility of menstruating. Even in women near or beyond the menopause he urges the supravaginal operation because the configuration of the vagina is better preserved and difficulties in coitus are eliminated, a fact to which the surgeons pay far too little attention. In the literature one of the reasons often given for performing total extirpation in young women is the opinion that if a stump remains, a cancer of the cervix can occur; he believes that this fear is greatly exaggerated, although he might consider this argument in older women.

at once and in addition stops the entire bloodflow from coming up through the cervix. The result is that when in addition the ovarian blood supply is controlled by ring forceps, the circulation through the uterus is completely stopped and the operation becomes bloodless. The incision in the uterus should be central and anterior whenever possible. Tumors situated off the midline can be reached by secondary incisions starting from the main incision and tunneling outward. Tumors lying in the posterior wall if not too large are removed "transcavity," the lumen of the uterus being opened from the front and the posterior wall being incised through the posterior endometrium. He states that there is no risk in opening the uterine cavity and it has the advantage of preventing small submucous fibroids being overlooked. Every fibroid down to the smallest seedling must be removed. A large fibroid in the posterior wall is handled through a transverse incision just behind the uterotubal junction. This incision opens the capsule of the tumor which is then extracted by morcellation after which the remaining posterior uterine wall is brought over the fundus and sutured anteriorly. This leaves a smooth posterior uterine wall opposed to the intestines, whereas if the fibroid is removed through an incision in the posterior wall, a suture line is left directly inviting intestinal adhesion.

In cases in which the number of fibroids to be removed is too great to allow the employment of either of the above methods, he performs a "block excision," bisecting the uterus down nearly to the internal os, removing the tumor area and then reuniting the remaining halves of the uterus. He has also developed a method of removing cervical fibroids by myomectomy, but from the opinions which will be quoted later in this review concerning cervical fibroids, it is doubtful if many gynecologists will adopt his method.

In the opinion of Zondek²⁰ the technique of myomectomy is much more difficult than that of hysterectomy, to which probably most gynecologists would subscribe. Hysterectomy has a typical technique but myomectomy is atypical; once the abdominal cavity is opened a plan must be made according to the case. It is not sufficient to remove the myomas but in addition it is important to spare the musculature as far as possible in order to preserve a uterus capable of its function in pregnancy and parturition. If the uterus following the operation is a slack, weak organ, it may be capable of menstruation but incapable of carrying a child and he believes that in such cases a high supravaginal amputation is a better procedure. In performing myomectomy he insists that every myoma must be enucleated, the orifice of one tube, preferably both tubes, must be spared, and the uterus must be reconstructed in such a manner as to preserve as much muscle tissue as possible. In order to test the last point he injects an ampule of pitocin into the reconstructed uterus. The reaction to this injection becomes apparent by the contraction and rigidity of the uterus and thus, according to the degree of contraction, the presence or absence of sufficient uterine musculature is demonstrated. He calls attention to the fact that it is possible to ligate the uterine artery on one side without interference with the nutrition of the uterus so that if such ligation becomes necessary in the course of a myomectomy, the surgeon should not assume that hysterectomy must follow. Myomectomy does give a much higher infection rate than hysterectomy because of the large

suggestion of malignancy in the uterus or if there is any infection present in the peritoneal cavity the blood should not be used. This method would be of value only in cases of very large tumors with greatly distended veins.

Uncommon Forms of Myoma. Ordinarily myomata are confined to the body of the uterus. Should hysterectomy be decided upon, the operation is well standardized, and usually presents few difficulties. In some of the uncommon forms of myoma, however, problems arise in their removal which may tax the skill of even the most experienced gynecologist. In considering the management of *intraligamentous myomas*, Counseller⁶⁶ refers to the type of tumor which grows out into the cellular tissues of the broad ligament. Since the uterine vessels enter the uterus near the internal os and since the most fixed point in the entire course of the ureter from the kidney to the bladder is closely associated with the tumor at this point, these structures are pushed laterally during the growth of the tumor and may present real difficulties during the operation, frequently resulting in an injury to the ureter. The veins are often enlarged from pressure and under tension, when free from blood, may resemble a ureter. In differentiating between the two, he reminds us that if a ureter is snipped or otherwise irritated with a thumb forceps, it forcibly contracts, distinguishing it from a blood-vessel. Any attempt to remove a large myoma in this location, without adequate exposure and without opening the broad ligament widely so that important structures can be seen will result in troublesome hemorrhage and perhaps injury to the ureter and bladder. It is his custom to open the broad ligament posteriorly, identify and retract the ureter at once so that any troublesome hemorrhage can be immediately controlled without fear of injury to the ureter. When a myoma extends from the posterior wall of the uterus far down behind the peritoneum of the cul-de-sac of Douglas, the ureters are both pushed laterally and the tumor grows upward in the mesentery of the sigmoid colon and the cecum. This type of tumor is often considered inoperable, but it can be removed by careful dissection after retraction of the blood-vessels in the fat of the mesentery of the colon. The safest method, according to Counseller, is to begin the removal by cutting through the peritoneum near the point of origin of the tumor and working laterally, always keeping in intimate contact with the wall of the tumor. A myoma on the lower anterior uterine wall may cause considerable distortion of the bladder. Counseller has found that the posterior wall of the bladder is often intimately attached to the fascial tissues adjacent to the fibroid, rendering difficult the separation of the fibroid from the bladder. If the bladder wall is injured during this separation, he has found it advisable to resect the wall of the bladder, leave it attached to the myoma and close the bladder with 2 rows of plain catgut. This is safer than to run the risk of development of a vesical fistula or secondary hemorrhage from the bladder.

Pedunculated submucous myomas should be removed only by vaginal myomectomy. If the patient has had children, adequate exposure is always possible, but if she is a nullipara it may be necessary to perform a deep lateral episiotomy. The tumor should be grasped with the hand and not with instruments, since such tumors are soft, friable and hemorrhagic. The cervix is usually large and soft enough to permit the index

He cannot understand why, in younger women, menstruation and the configuration of the vagina should be disturbed for prophylactic reasons only. It would not occur to any surgeon to remove the breast in a woman who had a mammary fibroma because later she might develop carcinoma.

In the large series reported by Danforth⁸ total hysterectomy was chosen only in those cases in which the cervix was noticed to be diseased or in which an early coincident cervical malignancy was suspected. He states that subtotal hysterectomy should always be preceded by careful study of the cervix and should only be done when the cervix is quite innocent in appearance. In expert hands the mortality of subtotal and total hysterectomy is about the same, but in the hands of the occasional operator the danger of injury to the bladder and ureters and the greater risk of contamination of the peritoneum increase the risk of operation considerably where total hysterectomy is employed. Therefore, he is of the opinion that frequent use of the more extended operation should not be made by those whose operative experience is small. Should the cervix present evidence of endocervicitis and ectropion, it is possible to do a cervical plastic procedure and a subtotal hysterectomy at the same sitting. By this means a healthy cervix may be left without the necessity of opening into the vagina from above. In cases in which nothing is done to the cervix at the time of operation, later cauterization may be helpful, particularly if some discharge persists. He believes that it is of great importance that at least one ovary be preserved, and that the operation should be carried out in such a way that the ovary will remain in good condition and continue to function. For this purpose it is necessary that a good blood supply be provided and the excision of the uterus carried out in such a manner that the hilum of the ovary with its contained vessels is not disturbed. If the ovary is left mobile the patient will be more comfortable than if it is fixed, therefore he does not attach the ends of the divided broad and round ligaments to the cervix unless it can be done without any tension.

In contrast to the foregoing opinions, in analyzing their series of 1001 cases of fibroids, Baer, Reis and DeCosta¹ state that the incidence of total hysterectomy in their practice has increased from 1.4% to 14.6% over a 10-year period. However, they still employ the supravaginal operation in over one-half of their cases so that they cannot be called enthusiasts over the total operation. Their report also shows that they tend to do fewer myomectomies. The use of radium has steadily diminished, having dropped from 15% to 2%. They remove one or both adnexa in about one-half of the cases. Since they have had a mortality of 0.21% in the last 484 consecutive patients, there can be little doubt but that their judgment and technique have been excellent.

An interesting technical advance has been reported by Wallingford¹⁸ consisting of giving the patient an autotransfusion with blood from a large myoma. After the blood supply to the tumor has been ligated, a needle is inserted into a large uterine vein and the blood aspirated into a citrate solution, filtered and injected into an arm vein, as much as 500 cc. being returned to the patient in this manner. The contraindications to the procedure are infection and malignancy, therefore it is advisable to collect the blood but not inject it until after the uterus has been removed and opened for a careful inspection. If there is any

between a pregnant uterus and one which is symmetrically enlarged due to a soft fibroid. At times even at operation a fibroid uterus is very soft and cystic and has the same color as a pregnant uterus. In case of doubt Greenhill⁹ advises studying the relationship of the round ligaments and tubes to the uterine mass. In a myomatous uterus there is usually asymmetry of the round ligaments and tubes, but if they are symmetrical in their relationships to the fundus the surgeon should manipulate the uterus to try to feel a fetus. If this gives no definite information he should inject pituitary extract directly into the uterine musculature. A pregnant uterus will quickly contract symmetrically and become whitish in color. A uterus containing a large fibroid will also contract and become blanched but usually not to the same extent. Furthermore, it may be possible to outline a fibroid distinctly from the main portion of the uterus. If the injection of pituitary extract fails to differentiate between a pregnant and a fibroid uterus, it is safe to cut down into the uterine musculature very gently and deliberately until it is certain that the thick muscle is due to a fibroid or until the bag of waters is seen bulging into the incision. If a fibroid is present, no harm has been done; even when a pregnancy is present, one may cut down to the bag of waters with impunity in most cases. If the incision exposes a pregnancy, it should be sutured and the uterus left intact. If during operation a pregnancy is found in a fibroid uterus, Greenhill believes that some or all of the fibroids should be removed and the gestation left undisturbed. If there are too many fibroids for enucleation, it is best to leave the uterus and the pregnancy alone and close the abdomen. At full term a Cesarean section may be performed and the uterus amputated at the same time.

Reis and Sinykin¹⁷ report 18 myomectomies performed during pregnancy without maternal mortality and with only 2 miscarriages. When performing myomeetomy during pregnancy they caution that the uterus be handled as little as possible; the myomectomy should be done with the uterus *in situ*. The uterine cavity should be avoided, as they are convinced that the incidence of postoperative miscarriage rises in direct proportion to the incidence of uterine cavity invasion. Careful hemostasis is necessary to insure a safe outcome. They believe in removal of only the guilty fibroid. In many instances fibroids are multiple, and it is a natural tendency to remove all of them; the authors state, however, that this is a serious mistake, since not only the patient but the pregnancy is much safer if the guilty fibroid alone is removed. They remind us that the majority of fibroids accompanying pregnancy require no treatment. The small group which shows evidence of acute degenerative changes, infection, hemorrhage, those pedunculated fibroids which undergo torsion, those which because of location encroach upon the birth canal, and those which undergo very rapid growth should be removed during pregnancy. The operation should be done at the time indications arise and irrespective of the age of the fetus. Such a procedure obviates the necessity of a Cesarean section followed by myomectomy or hysterectomy, a more complicated procedure than myomectomy followed by vaginal delivery.

When one is confronted with the complication of a fibroid and pregnancy at term Huber and Hesseltine¹⁰ advise that natural delivery should be allowed to go on unless the size, number or location of tumors

finger to be introduced along the pedicle to note its union with the uterine wall. It is rarely necessary to ligate the stump, but if bleeding is troublesome the uterus may be packed after the introduction of some antiseptic solution into the uterine cavity.

In considering *cervical fibroids*, Counseller and Collins⁷ observe that these tumors commonly affect multiparas, usually at or soon after the menopause. Their first sign is often the appearance of a sudden, large, alarming vaginal hemorrhage. The tumor may fill the pelvis, obstructing all the surrounding organs and often becoming adherent to neighboring structures, making surgical removal very difficult and dangerous. Local removal of either the smaller interstitial or pedunculated subserous types through the vagina may sometimes be done with ease and safety but the large interstitial tumors require an intra-abdominal approach and total hysterectomy. Recently in my own practice I had occasion to remove a very large cervical fibroid by total hysterectomy with all the usual technical difficulties and I was very glad to know that the incidence of these tumors is low, probably around 1%.

In reporting a case of *torsion of a fibromatous uterus*, McIver and Buxton¹² comment on its rarity. The infrequency of this complication is understandable, if one considers the stability of the normal uterus, supported by the broad and round ligaments. These ligaments prevent lateral torsion, though they permit anterior and posterior motion. When the uterus is enlarged and rises out of the pelvis, the cervical segment is elongated, the ligaments are stretched and the chance of torsion becomes greater. The case which McIver and Buxton report occurred in a 62-year-old woman. Acute symptoms and collapse were present. After preoperative transfusion, hysterectomy was performed under local anesthesia and the patient recovered. In these cases the tumor responsible for the twist is usually large, and the changes taking place in the uterus depend upon the extent to which the circulation is cut off; they vary from edema and congestion to actual necrosis. The torsion usually occurs at the isthmus, commonly from left to right and varies in extent from 90 to 450 degrees. These cases fall into two clinical groups: one giving the acute fulminating picture of a strangulated pedicle, while the other presents mild symptoms, without strangulation, which sometimes continue over a period of years. Prompt operation is indicated if the symptoms suggest strangulation.

Fibroids and Pregnancy. According to Charlewood⁴ fibroids undergo hypertrophy during pregnancy in response to hormonal influence. Such hypertrophy frequently outstrips the blood supply, and degeneration then occurs. Interstitial fibroids tend to be exteriorized by the contractions and thinning of the uterus during pregnancy. This exteriorization is another factor which tends to interfere with the blood supply and thus cause necrobiosis. The oligemic uterus of the puerperium is responsible for further degenerative changes in fibroids because of the reduced blood supply to the tumors. Moreover, the puerperal uterus grips interstitial and submucous tumors, thereby accentuating the anemic condition of the fibroids. These tumors involute after pregnancy in the same way as normal uterine tissue, sometimes becoming smaller than they were before the pregnancy because of the absorption of at least some of the necrosed tissue.

It is frequently impossible to differentiate on bimanual examination

to be followed by inhibition which is a much more enduring reflex. Both reflexes are eliminated by cutting the vagus nerves.

Records of single afferent fibers show the presence in the lungs of two distinct kinds of stretch receptors, one of which adapts slowly as described by Adrian, while the other kind adapts rapidly when inflation is maintained, usually dropping out of action within a second. The slowly adapting endings are on the average of lower threshold than the rapidly adapting endings, which do not come into action during normal quiet breathing.

Therefore the two kinds of response to inflation of the lungs may be explained by assuming that impulses from the slowly adapting receptors inhibit inspiration and that impulses from the rapidly adapting receptors excite inspiration. This interpretation of afferent function also accounts for excitation of inspiration by forced deflation of the lungs, for such deflation reduces the activity of many slowly adapting receptors, and many of the rapidly adapting receptors are stimulated by deflation as well as by inflation.

It is suggested that the rapidly adapting receptors are part of an autogenous pulmonary reflex mechanism, which increases the depth of any unusually deep inspiration, and permits very deep inspirations to be caused by relatively weak stimuli from other parts of the body.

Rôle of the Kidney in the Maintenance of Arterial Blood Pressure in Hemorrhage.* ANGIE S. HAMILTON and DEAN A. COLLINS (Department of Physiology, Temple University, School of Medicine). Since the kidney increases its production of pressor material in experimental renal hypertension, it appeared possible that this phenomenon might have a physiologic counterpart in conditions of stress altering renal circulation. To test this thesis for severe hemorrhage, three types of experiments were performed on over 50 dogs anesthetized with chloralose.

1. Animals without renal circulation were unable to maintain their blood pressures in hemorrhage as well as controls subjected to corresponding sham procedures. Thus a blood loss of 38 cc. per kg. in 50 minutes lowered the blood pressures of the two groups to averages of 23 and 63 mm. Hg respectively. Half of the animals without renal circulation died shortly after the conclusion of the hemorrhage. Since other known renal functions cannot explain these differences, they suggest the liberation of pressor material by the kidney.

2. Suggestive evidence was obtained that after extreme hemorrhage animals with intact renal circulation are partially or completely tachyphylactic to injected renin, while nephrectomized dogs are not.

3. Samples of blood from the renal vein and femoral artery were tested for pressor activity by injection into a nephrectomized animal. Both bloods collected before hemorrhage gave insignificant responses. After hemorrhage (34-45 cc. per kg.) renal vein and femoral artery bloods gave pressor responses of 15-28 and 9-13 mm. Hg respectively.

The above results support the thesis that the kidney liberates pressor material in hemorrhage and that this process constitutes a compensatory mechanism. This mechanism may be involved in hemorrhagic shock.

* Supported by a grant from the American Philosophical Society.

produces obstruction to the passage of the fetus. Trial of labor should be permitted in all doubtful cases. When operative interference prior to delivery is indicated by necrosis in the tumor, by obstruction to the birth canal or by failure of normal uterine mechanism, it should consist of Cesarean section with hysterectomy. If operative interference becomes necessary during the puerperium, hysterectomy is also the procedure of choice. They caution that myomectomy with Cesarean section carries a rather high mortality and its employment is generally contraindicated.

FRANK B. BLOCK, M.D.

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PHYSIOLOGY.

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Excitation and Inhibition of Inspiration by Distention of the Lungs. M. G. LARRABEE and G. C. KNOWLTON (Department of Physiology and Biophysics, Cornell Medical College, and Johnson Foundation, University of Pennsylvania). It has recently been shown by Worzniak and Gesell that in addition to the classical Hering-Breuer reflexes of inhibition of inspiration by distention of the lungs and excitation by their collapse, inspiration may also be excited by inflating the lungs. We have analyzed the afferent mechanisms of the two opposing reflexes elicited by lung inflation by recording the impulses discharged over single efferent fibers in the phrenic nerve and single afferent fibers in the vagus nerve of cats.

In order to excite inspiration the lungs must be distended to a volume exceeding the depth reached in normal quiet breathing, whereas very small inflations suffice to inhibit inspiration. When the lungs are rapidly inflated and then held at a volume sufficient to excite inspiration, the efferent discharge which is evoked lasts only about a second,

In a natural diver its regular usefulness in conserving oxygen is apparent. In a sloth the emergency situation is unusual, but it shows that it is possible for the level of metabolism to be depressed quickly in respiratory stress.

Correction. In the article by Coggeshall, Bennett, Warren and Bauer on "Synovial Fluid and Synovial Membrane Abnormalities . . ." in the October issue of this Journal (p. 486) the last word in the last sentence above Chart 3 on p. 490 should read "abnormal," instead of "normal." It should be noted also that Dr. Bennett's position in the School is Assistant Professor of Pathology, instead of Assistant Professor in Medicine.

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The Rôle of Carbonic Anhydrase in Certain Ionic Exchanges. M. H. JACOBS and DOROTHY R. STEWART (Departments of Physiology, University of Pennsylvania and Skidmore College). One of the authors (Cold Spring Harbor Symposia, 8, 30, 1940) has suggested a mechanism, analogous to chemical catalysis but involving a diffusion equilibrium rather than a chemical equilibrium, by which the rate of entrance of certain ammonium salts into the erythrocyte is greatly accelerated by low concentrations of bicarbonates (Ørskov: Pflüger's Arch., 231, 680, 1933). An essential part of the suggested mechanism is a cycle involving the conversion within the cell of CO_2 to HCO_3^- and the reverse change in the surrounding solution. A necessary consequence of such a theory would be an influence on the over-all rate of the process of the enzyme carbonic anhydrase. Such an influence, very striking in its magnitude, has been found, both by inactivating the carbonic anhydrase already present in the cells with KCN or sulfanilamide, and also by the addition under appropriate conditions of more of the enzyme to the surrounding solution. With concentrations of sulfanilamide approaching saturation, the bicarbonate effect may be almost completely (but reversibly) abolished without greatly altering the general osmotic properties and permeability of the cell. Under properly chosen conditions a measurable inhibition can be demonstrated with concentrations of sulfanilamide as low as a few hundredths of a milligram per 100 cc. Sulfapyridine seems completely to lack this inhibitory power. By the same general methods the principle of catalysis of diffusion by bicarbonates can be extended to the volume changes of erythrocytes which occur on altering the pH of the medium, and also to exchanges of Cl^- from the erythrocyte for SO_4^{2-} from the surrounding medium. There is reason to believe that bicarbonates and carbonic anhydrase may also behave in a similar manner in certain tissues other than the blood.

The Depression of Metabolism During Diving. LAURENCE IRVING, P. F. SCHOLANDER and S. W. GRINNELL (Edward Martin Laboratory, Swarthmore College). It has been shown that the use of oxygen by seals during recovery from a dive frequently fails to compensate for the lack of oxygen use during the dive (Scholander, P. F., Hvalraadets Skrifter, No. 22, Det Norske Videnskaps Akademi i Oslo, pp. 1-129, 1940). A decline of body temperature has also been observed during a dive, and the two observations support the view that the level of metabolism of the seal is depressed during diving.

The possibility that the metabolic rate of a mammal can thus be quickly depressed was tested in studies of the three-toed sloth, *Bradypus tridactylus*, at Barro Colorado Island, Panama Canal Zone. The sloths easily endured repeated submersions for 20 minutes. Measurements of respiratory metabolism were recorded by Scholander's difference respirometer. In recovery from dives, there was very little or no extra use of oxygen to indicate a restitution of any considerable anaërobic process. The small lactic acid formation in the dive had practically disappeared after 10 minutes recovery. It is thus shown that the metabolism of the sloth is very much depressed during a dive. The reduction conserves oxygen stores and is of regular occurrence in seals.

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